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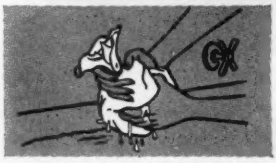

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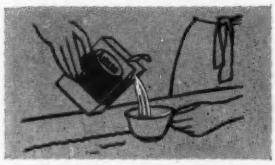

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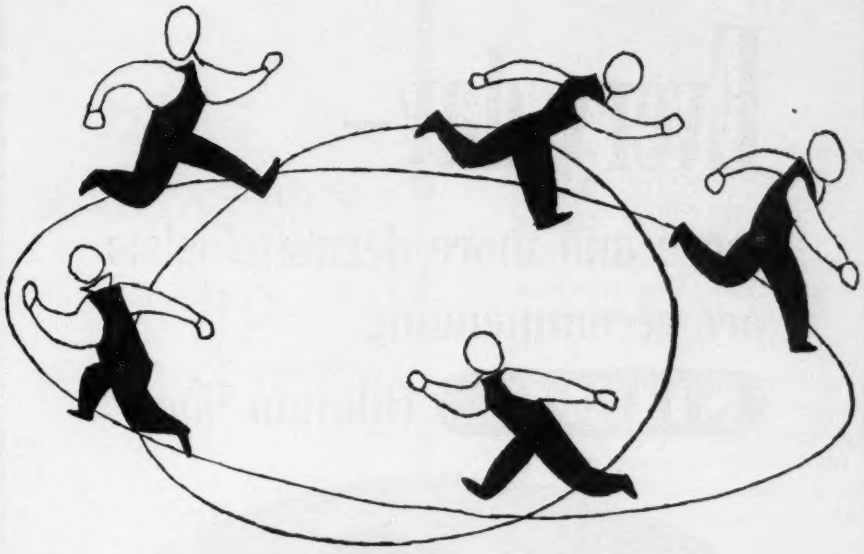

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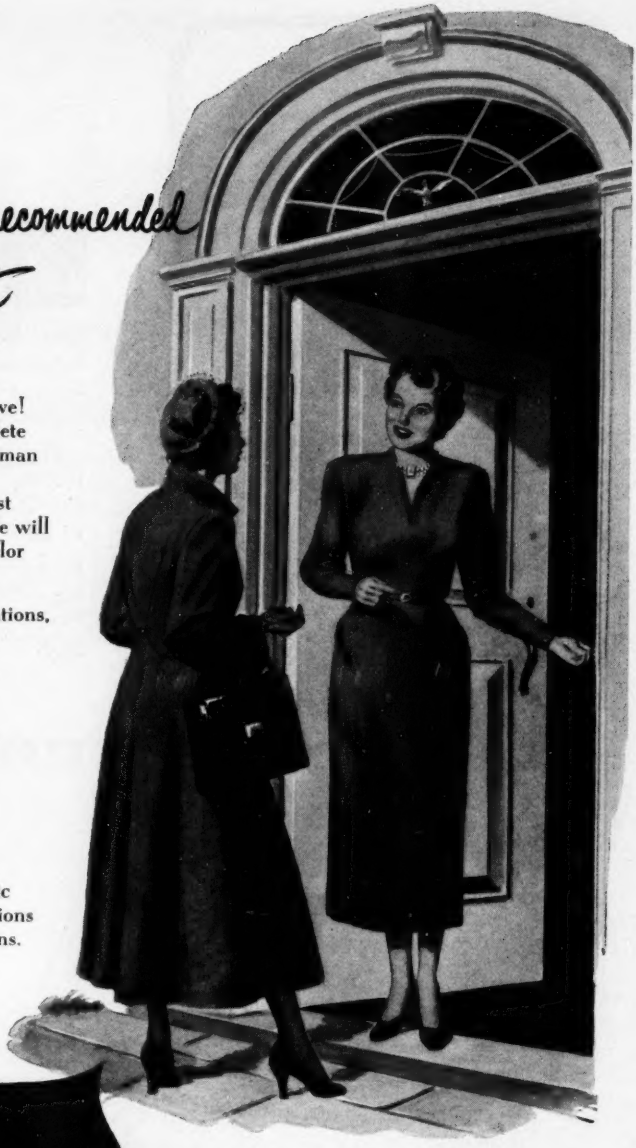

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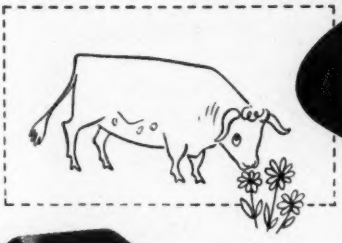

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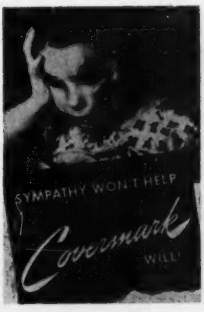

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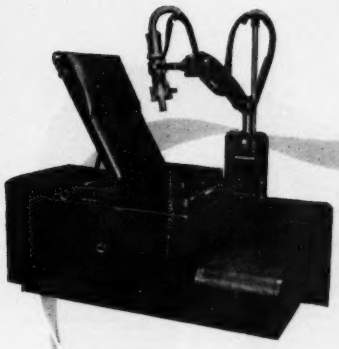

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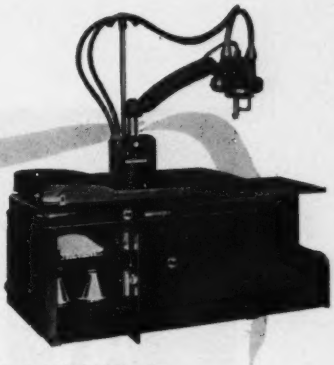

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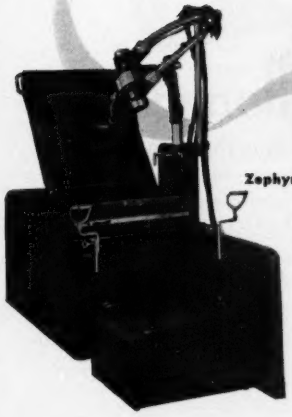

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CONTENTS

PAGE

Is Mycosis Fungoides a Reticuloendothelial Neoplastic Entity? EDWARD P. CAWLEY, M.D.; ARTHUR C. CURTIS, M.D., AND JAMES E. K. LEACH, M.D., ANN ARBOR, MICH. ... 255

Rise and Growth of Dermatology in New York. PAUL E. BECHET, M.D., ELIZABETH, N. J. ... 273

Ferdinand von Hebra: In Commemoration of His Appointment One Hundred Years Ago as Professor of Dermatology at the University of Vienna. ERNEST SPITZER, M.D., ST. LOUIS ... 282

The Treatment of Granuloma Inguinale, Lymphogranuloma Venereum, Chancroid, and Gonorrhea. HARRY M. ROBINSON JR., M.D., BALTIMORE ... 284

Clinical Studies in Percutaneous Absorption. M. V. NADKARNI, PH.D.; DONALD B. MEYERS, PH.D.; ROBERT G. CARNEY, M.D., AND LOUIS C. ZOPF, M.S., IOWA CITY ... 294

Keratosis Punctata Palmaris et Plantaris. MICHAEL J. SCOTT, M.D.; MAURICE J. COSTELLO, M.D., NEW YORK, AND SOCORRO SIMUANGCO, M.D., MANILA, PHILIPPINES ... 301

Occurrence of Microsporum Gypseum (M. Fulvum) Infections in the District of Columbia Area: Report of Six Cases. CAPTAIN E. RANDOLPH TRICE, MEDICAL CORPS, UNITED STATES ARMY, AND JUNE CAROL SHAFER, M.D., ARLINGTON, VA. ... 309

Hypertrophic Lichen Planus in West African Negroes. G. H. V. CLARKE, M.A., M.B.B.S., A.R.I.C., M.R.C.S., LAGOS, NIGERIA ... 314

Successful Treatment of Pemphigus with Heparin. JOHN P. MAGNER, M.D.; R. CAMPBELL MANSON, M.D., AND ALLEN PEPPLE, M.D., RICHMOND, VA. ... 320

Use of the Hypospray® in Dermatology. ROBERT H. PRESTON, M.D.; LEON GOLDMAN, M.D., CINCINNATI, AND LIEUTENANT COLONEL ROBERT G. THOMPSON, MEDICAL CORPS, ARMY OF THE UNITED STATES ... 327

Lichen Simplex Chronicus and Its Variants: A Discussion of Certain Psychodynamic Mechanisms and Clinical and Histopathologic Correlations. BERTRAM SHAFFER, M.D., AND HERMAN BEERMAN, M.D., PHILADELPHIA ... 340

Primary Involvement of the Upper Extremities in Thromboangiitis Obliterans. EUGENE M. FARBER, M.D., AND MILLARD H. MCLAIN, M.D., SAN FRANCISCO ... 352

Fixed Drug Eruption from Aureomycin: Report of Two Cases. ASHTON L. WELSH, M.D., AND LAWRENCE C. GOLDBERG, M.D., CINCINNATI ... 356

CLINICAL NOTES:

Periarteritis Nodosa: Report on a Patient Treated with Paraaminosalicylic Acid. LEE CARRICK, M.D., AND E. C. VONDER HEIDE, M.D., DETROIT ... 359

Trial of Some Adenosine Compounds in Pruritus. CARL M. PEARSON, M.D., AND JOHN L. FROMER, M.D., BOSTON ... 362

Spontaneous Cure of Tinea Capitis Due to Microsporon Audouini. WILLIAM E. LAUR, M.D., AMARILLO, TEXAS ... 364

Vitiligo in (Apparent) Dermatomal Distribution. JUD R. SCHOLTZ, M.D., AND CRAIG WILLIAMSON, M.D., PASADENA, CALIF. ... 366

Simple Method of Making X-Ray Shields for Small Ports. JEFF DAVIS, M.D., AND EVA DAVIS, B.S., NEW YORK ... 369

Water-Removable Paste. CLINTON G. BEIRNE, M.D., AND GILBERT A. BEIRNE, M.D., SAN FRANCISCO ... 370

Unusual Sequela to Chrome Ulceration of the Skin. WALTER F. EDMUNDSON, M.D., WASHINGTON, D. C. ... 371

Herpes Zoster Treated with ACTH. WALTER R. NICKEL, M.D., SAN DIEGO, CALIF. 372

SOCIETY TRANSACTIONS:

Detroit Dermatological Society ... 373

Cleveland Dermatological Society ... 374

Philadelphia Dermatological Society ... 378

NEWS AND COMMENT ... 384

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IS MYCOSIS FUNGOIDES A RETICULOENDOTHELIAL NEOPLASTIC ENTITY?

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MYCOSIS fungoides was first described by Alibert (1812),[1] who labeled the disease *pian fungoide* because some of the cutaneous lesions resembled those of yaws. Later (1835)[2] he substituted the word "mycosis" for "pian" to describe the remarkable mushroom-like tumors but had no intention of suggesting that the disease was caused by fungi. In 1851, Bazin gave an admirable account of the clinical features of mycosis fungoides, and 13 years later Köbner described the disease as a "granuloma." Ranvier (1869) and Hebra (1872) were early contributors to knowledge of the histology of the disorder, and Auspitz (1885)[3] first employed the term "granuloma fungoides." The striking *d'emblée* form of mycosis fungoides was recognized by Vidal and Brocq in 1885. Eight decades after Alibert's original contribution, Besnier and Hallopeau (1892)[4] described the premycotic, erythematous stage of mycosis fungoides. In later years a great many investigators have been keenly interested in this extraordinary disease and have further explored and clarified many of its perplexing aspects.

MYCOSIS FUNGOIDES

The name mycosis fungoides and its synonym granuloma fungoides are inept, because the first implies a mycotic etiology and the second intimates that the disease is an inflammatory reaction of the reticuloendothelial system. Both names are expressive, however, and are the common terms by which the disease is usually described.

The exact cause of mycosis fungoides remains uncertain in spite of diligent research devoted to the subject. Within recent years the pendulum of dermatological

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1. Stelwagon, H. W.: A Treatise on Diseases of the Skin for Advanced Students and Practitioners, Philadelphia, W. B. Saunders Company, 1916.

2. Kaposi, M.: Pathologie und Therapie der Hautkrankheiten: in Vorlesungen für praktische Aerzte und Studirende, Wien, Urban & Schwarzenberg, 1893.

3. Sequeira, J. H.: Discussion on Mycosis Fungoides, Brit. J. Dermat. **26**:213 (May) 1914.

4. Besnier, E.; Brocq, L., and Jacquet, L.: La pratique dermatologique, Paris, Masson & Cie, 1902.

opinion has swung away from an infectious cause and has placed the disease quite securely among the lymphoblastomas, thus emphasizing its probable neoplastic nature. A recent experiment attempting the transmission of mycosis fungoides from humans to mice indicates, however, that the possible role of infection cannot be lightly dismissed.[5] Mycosis fungoides of spontaneous origin has been reported in at least one animal (the cow),[6] but such an event is extraordinarily rare.

Fig. 1.—Alibert's original case of *pian fungoide.*

CLINICAL FEATURES

For purposes of description mycosis fungoides is divided into three stages: first, the premycotic or erythematous stage; second, the plaque or infiltrative stage; and third, the tumor or fungoid stage. The first is characterized by red, scaly, and often nondescript lesions simulating other diseases at various times. Infiltrated plaques characteristic of the second stage are superimposed in some instances on

5. Stratton, E. K.: Report of a Case, with Clinical, Postmortem and Experimental Observations, Arch. Dermat. & Syph. **48**:179 (Aug.) 1943.

6. Hofstra, L.: Mycosis (granuloma) fungoides, Tijdschr. Diergeneesk. **71**:283 (June 1) 1946; abstracted, Excerpta Medica (Sect. 13) **1**:53 (April) 1947.

pre-existent lesions but frequently develop on clear skin. These plaques may be few or many and are often remarkable because of their bizarre configuration and vivid coloration. They are round, oval, horseshoe-shaped, angular, linear, or serpiginous, and their color varies from some shade of red to purple. Pruritus may be an outstanding symptom with the first two stages. The tumors of mycosis fungoides occur by predilection on the trunk, although any part of the integument may be involved. Their size varies considerably, some being as large as an orange, and their color is usually reddish purple. Numerous examples of mycosis fungoides *d'emblée*, characterized by the sudden appearance of one or more tumors without antecedent premycotic or infiltrative stages, have been recorded. Most but not all tumors of mycosis fungoides ulcerate at some stage of their evolution.

DIAGNOSIS

The diagnosis of mycosis fungoides is based on a combination of clinical features and pathological studies. It is worth emphasizing, however, that a period of observation is sometimes necessary before the diagnosis can be established with certainty. Clinically, eczema, psoriasis, seborrheic dermatitis, erythema multiforme, and exfoliative dermatitis are the diseases most frequently mimicked by mycosis fungoides in the premycotic stage. The bizarre, gyrate, and configurate plaques which present themselves in the second stage are distinctive and seldom confused with other disorders. The tumors of the third stage may resemble those of leukemia, leprosy, sarcoma, or metastatic melanoblastoma, but the coexistence of other lesions of mycosis fungoides is usually sufficient to suggest the diagnosis. Cases in which the *d'emblée* form of mycosis fungoides has been isolated under the mistaken diagnosis of leprosy are on record.[7]

The microscopic alterations of mycosis fungoides have been the basis for much of the dispute as to the exact nature of the disease. Epidermal changes occur, including acanthosis, the formation of micro-abscesses containing lymphocytes (Pautrier abscesses), intercellular edema, dissolution of the basal layer, and atrophy of the epidermis when it overlies a tumor. These findings are of secondary importance, however, and it is only the dermal infiltrate which may be of diagnostic significance. In the premycotic and plaque stages of mycosis fungoides this infiltrate is usually found in the upper third of the dermis. Its cellular components may be diverse, including reticuloendothelial cells, connective-tissue cells, lymphocytes, mast cells, polymorphonuclear leukocytes, eosinophils, monocytes, and plasma cells. The infiltrate is commonly distorted by pyknosis and karyorrhexis, and clumping of reticuloendothelial cells occurs, with formation of pseudo-giant-cells. The multiplicity of cell types, their distortion, and the clumping are listed as cardinal features in the microscopic diagnosis of mycosis fungoides but cannot always be demonstrated, even in otherwise authentic cases of the disease. In the tumor stage the infiltrate is diffuse and may occupy the entire dermis. It is commonly monomorphous in its cellular architecture, being composed of reticuloendothelial cells. There is a paucity of information regarding the worth of other laboratory studies in the diagnosis of mycosis fungoides.

7. Carrillo, F. P.: Aproposito de un caso de micosis fungoides, Rev. argent. dermatosif. **30**:161, 1946; abstracted, Excerpta Medica XIII **1**:133 (May) 1947.

The present paper is based on a review of the cases of 10 patients studied at the Dermatology Service of the University Hospital who had diagnoses of mycosis fungoides and were subsequently examined at necropsy and is concerned with the nosology of mycosis fungoides and some of its clinical and laboratory features which have remained obscure.

REPORT OF THE CASES

CASE 1.—L. B., a white male foundry worker aged 55, first noticed the gradual onset of asymptomatic, erythematous papulosquamous lesions on his trunk, thighs, and upper arms at the age of 12. These persisted without change until November, 1944, 43 yr. after the appearance of the eruption, at which time there was a sudden and rapid increase in the size and depth of the lesions and, simultaneously, the onset of severe pruritus. Nodules and tumors appeared, and some of the latter became ulcerated. In January, 1945, he began to notice dyspnea on exertion.

On April 9, the patient was admitted to the University Hospital. He had an almost universal eruption which consisted of erythematous, papulosquamous lesions, indurated plum-colored plaques of variable size and configuration, and scattered bluish-red, mushroom-like tumors. The heart was enlarged, and auricular fibrillation was present. There were numerous palpable lymph nodes in the axillae and inguinal regions. Complete examination of the blood showed a sedimentation rate of 26 mm. an hour on one occasion and an eosinophil count of 13% on another, but the results were not significant otherwise. Roentgenograms revealed generalized moderate cardiac enlargement. A skin biopsy of one of the tumors showed a band-like infiltrate in the upper third of the corium composed of reticuloendothelial cells.

The patient died on September 2. Microscopic examination showed numerous and extensive neoplastic infiltrations in the myocardium, lungs, bronchial lymph nodes, and liver and neoplastic replacement of rib, sternal, and vertebral marrow, spleen, and periaortic lymph nodes. The neoplasm in all these sites was composed of giant cells of the Reed-Sternberg type, many hyperplastic reticuloendothelial cells, lymphocytes, occasional plasma cells, and a few eosinophils. Several areas of necrosis were found in the periaortic lymph nodes.

CASE 2.—M. K., a white male farmer aged 54, was admitted to the University Hospital on Jan. 24, 1940. About six years previously he had noted the gradual appearance of a palm-sized, erythematous, slightly pruritic plaque on the right flank. This lesion remained stationary for about two years, after which several others with similar characteristics but varying considerably in size developed on the back, thighs, and right side of the abdomen. Two months before admission, paroxysmal itching and burning of the skin occurred. There were intermittent episodes of severe abdominal pain, and his general health began to deteriorate.

Examination at the time of admission revealed a huge, bluish-red, infiltrated plaque which involved most of the back and extended onto the abdomen and chest. On the buttocks were several circumscribed indurated lesions. Enlarged lymph nodes were noted in both axillary regions and in the left inguinal area. A biopsy from the large plaque on the back showed a dense neoplastic cellular infiltrate in the corium. The predominant cells in the infiltrate were reticuloendothelial cells. Eosinophils were fairly abundant, as were also lymphocytes. The results of several complete blood studies were normal.

Respiration ceased on March 13. Microscopic examination showed extensive lymphoblastomatous infiltrations of the corium and subcutaneous tissues of several specimens of skin. The axillary, inguinal, periaortic, and retroperitoneal lymph nodes were completely replaced, and the appendix and periureteral adipose tissue thoroughly infiltrated by the neoplasm. The lymphoblastoma in all sites was composed exclusively of reticuloendothelial cells.

CASE 3.—M. R., a white housewife aged 32, was first seen on May 9, 1920, and hospitalized. She had been as well as usual until 13 mo. previously, at which time pruritic patches which she described as "eczema" appeared on the abdomen. Nodules and tumors developed in these patches. Some of the tumescences disappeared spontaneously but were replaced by others.

Examination showed an almost universal eruption which consisted of scaling patches, infiltrated plaques, and large tumors, some of which were ulcerated. There was generalized lymphadenopathy. The blood picture on several occasions was characterized by a persistent moderate increase in eosinophils but was otherwise normal. A biopsy from the border of an

ulcerating lesion on the back revealed a massive infiltrate in the dermis consisting of reticuloendothelial cells, occasional lymphocytes, young connective-tissue cells, and abundant eosinophils.

The patient died on May 20. Anatomically the lymphoblastoma was found to involve the skin, spleen, bone marrow, and lymph nodes. All skin specimens showed evidence of lymphoblastoma, but the cellular architecture was notably altered from that encountered in the biopsy. Reticuloendothelial cells, lymphocytes, and fibroblasts predominated, and there were occasional large, dark-staining multinucleated cells which resembled Reed-Sternberg cells. Eosinophils were conspicuous by their absence. The neoplasm in the spleen, lymph nodes, and bone marrow was composed of reticuloendothelial cells with a scattering of the large, multinucleated cells.

CASE 4.—G. M., a white male mechanic aged 67, was admitted to the University Hospital on Jan. 6, 1933. He stated that he had had generalized pruritus, but no evidence of a skin eruption, for about three years. Four months previous to his first visit, vesicles and pustules appeared on the neck and gradually spread to the face, hands, and feet.

Examination revealed generalized erythema, numerous excoriations, and vesicopustules of variable size on the dorsa of the hands. There were palpable nodes in the cervical and inguinal regions and both axillae. Numerous widespread vesicles and bullae appeared, and the diagnosis of pemphigus was considered. A biopsy from the margin of one of the bullae showed reticuloendothelial cells in the dermis which had clumped in some areas to form pseudo-giant-cells and a few lymphocytes. There was a gradual appearance of scattered, configurate plaques, nodules, and tumors. Examination of the blood was repeated frequently and on one occasion showed 27% eosinophils.

The patient's course was progressively downhill, and he died on April 7, 1936. Skin specimens disclosed extensive lymphoblastomatous infiltrations, but the neoplastic cells at this time were immature lymphocytes. There were also partial lymphoblastomatous replacement of bone marrow and cervical lymph nodes and lymphoblastomatous infiltrations in the aortic adventitia, kidneys, adrenals, and dura mater with the same type of neoplastic cells.

CASE 5.—M. M., a white housewife aged 28, was admitted to the University Hospital on May 21, 1931. She had had severe pruritus of the skin of her entire body for the preceding seven years, and for one year prior to admission her skin had been a bright-red color. In 1926, she had been seen as an outpatient with a typical infiltrated plaque of mycosis fungoides on the inner aspect of her left thigh. This lesion and several others which developed later underwent spontaneous involution but were followed by new similar patches. Her mother had died of mycosis fungoides at the age of 49.[8]

Examination revealed generalized erythema, several large indurated plaques, and many excoriations. A generalized lymphadenopathy was present, and the spleen was palpable. A biopsy from an erythematous patch of skin showed perivascular-reticuloendothelial cell proliferation and extensive lymphocytic infiltration. Examination of the blood showed 19% eosinophils on one occasion and a few pathological lymphoid cells on another. In January, 1938, a granular parenchymal infiltration of the lower two-thirds of the right lung, interpreted as bronchopneumonia, and left pleural effusion were visualized by roentgenogram.

Respiration ceased on February 12. All skin specimens disclosed extensive lymphoblastomatous infiltrations, as did also the spleen, lymph nodes, liver, kidneys, bone marrow, diaphragm, and breasts. Acute fibrinopurulent bronchopneumonia of the right middle and lower lobes of the lungs was present in conjunction with extensive lymphoblastomatous infiltration of the same sites, and there was massive left hydrothorax with atelectasis of the left lung. The neoplastic cells were chiefly lymphoblasts, but there were also large numbers of eosinophilic leukocytes.

CASE 6.—M. S., a white housewife aged 69, gave a history of generalized pruritus for 10 yr., a recurring "eczematoid dermatitis" for three or four years, and several cutaneous plaques and tumors for the preceding six weeks at the time of admission to the University Hospital on Nov. 23, 1942. She had lost a few pounds in weight, and her strength had ebbed during the preceding month or two.

Examination revealed numerous brick-red, elevated and indurated, scaling cutaneous plaques of variable size. On the thighs there were ulcerated tumors. The blood cell count was normal

8. Cameron, O. J.: Mycosis Fungoides in Mother and in Daughter, Arch. Dermat. & Syph. **27**:232 (Feb.) 1933.

on several occasions. In roentgenograms the left lung showed changes suggestive of bronchial pneumonia. A biopsy taken from an infiltrated plaque on the arm showed a dense infiltrate in the dermis composed almost exclusively of atypical cells which appeared to be lymphoblasts.

The patient's general condition deteriorated steadily, and she died on December 20. Microscopic examination revealed lymphoblastomatous focuses in the spleen and peribronchial and retroperitoneal lymph nodes, and extensive infiltration of the left lung and skin. The neoplastic cells were lymphoblasts.

CASE 7.—C. M., a white housewife aged 67, stated that she had received electrical-shock therapy for a psychosis in 1942 following which a dry, pruritic scaling eruption developed on the dorsum of the trunk. The eruption persisted and became more extensive until the entire cutaneous surface was eventually involved. The family history was notable because of the following: one sister of the patient was said to have had leukemia, another sister pernicious anemia, and a nephew was also reported to have had leukemia.

Examination at the time of admission on Jan. 3, 1948, revealed a universal, exfoliative, erythematous eruption with generalized thickening of the skin. On the lateral chest walls, as well as in the axillae and inguinal regions, were large indurated plaques and tumors, some of which were ulcerated. The scalp was covered with a yellowish scale, and there was thinning of the scalp hair with some areas of complete alopecia. There was generalized lymphadenopathy, and the spleen was palpable. Repeated examination of the blood showed it to be normal except for a sedimentation rate of 23 mm. an hour on one occasion. A skin biopsy from a plaque showed a dermal infiltrate which contained lymphoblasts, reticuloendothelial cells, and occasionally eosinophils.

The patient died on February 18. Seven specimens of skin were removed, including two from the scalp. The microscopic observations in all were similar to those in the biopsy except for a preponderance of reticuloendothelial cells and the absence of eosinophils and lymphoblasts. Structures other than the skin were not found to be involved by the lymphoblastoma.

CASE 8.—R. H., a white housewife aged 60, was admitted to the University Hospital on Aug. 18, 1943, and gave the following history: For many years she had had several erythematous maculopapules on the abdomen. In 1938, these lesions began to enlarge and became covered with scale. Subsequently, over a period of years, the skin of the entire body was similarly involved. About two years before admission an ulcerated lesion appeared on the forehead. This healed but was followed by numerous similar lesions about the head and face. Pruritus had been a distressing symptom.

The patient had a universal scaling erythroderma and scattered maculopapules of variable size. There were several large, indurated ulcers on the forehead and right side of the face. Scalp hair was sparse. Complete blood examination on several occasions gave normal results, with the exception of a persistent eosinophilia of 6%. Four specimens of skin for microscopic examination showed only the changes of a severe, long-standing dermatitis. The clinical diagnosis of mycosis fungoides could not be substantiated by these observations.

Respiration ceased on June 27, 1944. Six specimens were taken from the skin. Four of these showed evidence of a severe, nonspecific dermatitis. Two others revealed a polymorphous cellular infiltrate in the upper dermis of the type described as characteristic of mycosis fungoides. Internal evidence of lymphoblastoma was not found.

CASE 9.—C. C., a 65-yr.-old white male prison inmate, was admitted to the University Hospital on Jan. 25, 1938. Six months previously he had been seen by a competent dermatologist in another city because of numerous scattered, indurated lesions of the skin. A clinical diagnosis of mycosis fungoides had been made at that time and reportedly confirmed by a biopsy. He was subsequently confined to a penitentiary.

At the time of admission, the scalp had a cerebriform appearance, fashioned by numerous infiltrated convolutions separated by furrows. The ears were tremendously enlarged, and the skin of the neck, upper trunk, and arms was erythematous and thickened. There were vivid purplish plaques and tumors on the hands, forearms, and thighs and an ulcerated nodule at the right corner of the mouth and another behind the right ear. Inguinal, axillary, and cervical lymph nodes were markedly enlarged. Examination of the blood on one occasion showed 12% neoplastic cells which did not belong to the ordinary types of blood cells and were referred

to as those of an hemocytoblastoma but could not be further identified by the hematologist. Specimens of skin showed a dense, monomorphous infiltrate involving the corium and composed of reticuloendothelial cells.

The patient died on February 8. Microscopic study disclosed extensive lymphoblastomatous infiltrations in the skin, white inguinal, axillary, cervical, and retroperitoneal lymph nodes were partially replaced and submucosal tissues of the tongue infiltrated by the lymphoblastoma. The neoplasm was composed of reticuloendothelial cells. Marrow of the sternum, a rib, and a vertebral body contained a large proportion of the same type of neoplastic cells.

CASE 10.—H. I., a white male farmer aged 72, was admitted to the dermatology service in November, 1923. At the time of his first examination, on Jan. 16, 1922, he was found to have an irregular area of ulceration at the junction of the hard and soft palate which was indurated and bled easily on manipulation. On Aug. 29, 1923, generalized flattened nodular and infiltrated cutaneous plaques of variable size and configuration which were associated with pruritus were noted to have developed. In addition, the left testicle was swollen to the size of a small orange and was of boardlike consistency.

At the time of admission in November, the clinician made a diagnosis of mycosis fungoides and implicated the oral lesions as part of the process. Repeated blood cell counts were normal. Microscopic examination of a biopsy from one of the infiltrated nodules on the back revealed a dermal infiltrate containing many large closely packed lymphoblasts and large numbers of plasma cells.

Respiration ceased on Jan. 31, 1924. At autopsy gross evidence of lymphoblastoma was found in the skin, heart, tonsils, salivary glands, thyroid, gastrointestinal tract, pancreas, and kidneys, in the mediastinal, bronchial, mesenteric, and retroperitoneal lymph nodes, and in the left testis and urinary bladder. Microscopic examination of all these tissues showed a lymphoblastoma composed of lymphoblasts and a great many plasma cells. Several of the neoplasms in the lymph nodes contained abundant giant cells of the Reed-Sternberg type which were indistinguishable from those which are found in Hodgkin's disease. Eosinophils were not seen.

Comment on the Cases.—Age, Sex, Race, and Familial Incidence: Of the 10 patients, two were under the age of 35, two were between 50 and 60, and the remainder were more than 60 at the time the diagnosis of mycosis fungoides was established. An example of the *d'emblée* form of the disease in a newborn infant has recently been reported,[9] but in general mycosis fungoides is a disease of the late decades of life. There was an equal division of the 10 patients as to sex. It is usual, however, for men to be affected oftener than women.[10] Patients of varied racial extraction were numbered among the 10 cases. Mycosis fungoides is not as rare in the Negro race as was formerly believed,[11] and it has been shown that there are no significant differences between mycosis fungoides in white and in Negro patients.[12] The family history was notable in Case 5 because this patient's mother had also died of mycosis fungoides [8] and in Case 7 because of the occurrence of two cases of leukemia and one of pernicious anemia in the patient's family.

Clinical Features: The onset of the disease was insidious in almost every instance. At the time of admission to the hospital cutaneous lesions had been present in one patient (Case 9) for only six months and in another (Case 1) for

9. Serra, J. B.; Venuti, A., and Castane, D.: Micosis fungoides en un lactante, Rev. argent. dermatosif. **30**:163, 1946; abstracted, Excerpta Medica XIII **1**:133 (May) 1947.

10. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943.

11. Strobel, E. R., and Hazen, H. H.: Mycosis Fungoides in the Negro, J. Cutan. Dis. **29**:147, 1911. Hazen, H. H.: Mycosis Fungoides and Similar Conditions in the Negro, Arch. Dermat. & Syph. **55**:111 (Jan.) 1947.

12. Sigel, H.: Mycosis Fungoides in the Negro, Arch. Dermat. & Syph. **52**:18 (July) 1945.

43 yr. The abrupt evolution of severe pruritus in papulosquamous lesions which had been asymptomatic for 43 yr. (Case 1) intimates that metamorphosis of parapsoriasis en plaque to mycosis fungoides may have taken place. Opinion is divided, however, as to whether such transformations actually occur or whether some patients have an attenuated form of mycosis fungoides for many years without progression of the disease.[13] One patient (Case 2) had a solitary lesion or "herald patch," as occurs in pityriasis rosea, for two years before the eruption became widespread. Pruritus was the conspicuous symptom in every case and antedated the appearance of cutaneous lesions by three years in Case 4, two years in Case 5, and six years in Case 6. Intermittent episodes of severe abdominal pain caused by retroperitoneal lymphadenopathy occurred in Case 2. In all instances the cutaneous lesions were the first to attract attention, although at the time of admission to the hospital several patients (Cases 1, 2, 3, 4, 5, and 9) had palpable lymphadenopathy, proved at necropsy to be part of the disease.

The earliest lesions of mycosis fungoides were eczematoid in two patients (Cases 3 and 6), papulosquamous in three (Cases 1, 7, and 8), plaquelike in two (Cases 2 and 9), universal erythematous in one (Case 5), vesicular and bullous in one (Case 4), and involved mucous membranes adjoining the cutaneous surface in one (Case 10). Vesicular or bullous mycosis fungoides is exceptionally rare, but previous examples have been recorded.[14] Mucous-membrane involvement, as occurred in Case 10, is also distinctly uncommon, although this point has been little emphasized. Verrucose and hyperkeratotic lesions of mycosis fungoides, which simulate tuberculosis verrucosa cutis and are another rare and little known cutaneous manifestation of the disease,[15] were not encountered in this series.

Fever was an inconspicuous feature in all 10 patients and could be accounted for solely on the basis of secondary infection. In some instances [16] persistent fever of severe and debilitating degree, apparently a manifestation of the disease itself, has been reported.

Mushroom-like tumors developed in four patients (Cases 1, 3, 6, and 9). It is quite possible that x-ray therapy held the tumors in abeyance in some of the others. No examples of mycosis fungoides *d'emblée* were encountered in this series.

It is worth noting that nearly all cases of mature mycosis fungoides present a conglomeration of cutaneous lesions and also that the three stages of the disease

13. Keil, H.: Parapsoriasis en Plaques Disseminees and Incipient Mycosis Fungoides, Arch. Dermat. & Syph. **37**:465 (March) 1938. Montgomery, H., and Burkhart, R. J.: Parapsoriasis: Its Relation to Mycosis Fungoides and Tuberculosis: Review of 52 Cases, ibid. **46**:673 (Nov.) 1942.

14. Garb, J., and Wise, F.: Mycosis Fungoides with Bullous Lesions, Arch. Dermat. & Syph. **48**:359 (Oct.) 1943. Ormsby, O. S., in discussion on Wile, U. J.: Mycosis Fungoides, ibid. **36**:903 (Oct.) 1937. O'Leary, P., in discussion on O'Leary, P.; Montgomery, H., and Brunsting, L. A.: Presentation of Cases, ibid. **31**:403 (March) 1935. Belote, G. H., in discussion on Wile, U. J.: Mycosis Fungoides, ibid. **33**:387 (Feb.) 1936. Wile, U. J., and Knerler, C. W.: Mycosis Fungoides in Mother and Daughter: Further Report, ibid. **38**:939 (Dec.) 1938. Lortat-Jacob, L., and Legrain, P.: Mycosis Fungoides with Bullous, Ulcerative Elements, of Cyclic or Polycyclic Arrangement, Bull. Soc. franç. dermat. et syph. **33**:623, 1926.

15. Jeanselme, E., and Burnier: Verrucose and Hyperkeratotic Form of Fungoid Mycosis, Ann. de dermat. et syph. **7**:65 (Feb.) 1926.

16. Post, C. F., and Lincoln, C. S.: Mycosis Fungoides: Report of 2 Unusual Cases with Autopsy Findings, J. Invest. Dermat. **10**:135 (March) 1948.

comprise artificial subdivisions which frequently do not present themselves in orderly sequence. These facts are borne out in review of the cases of the 10 patients.

Significant physical findings produced by the disease, and exclusive of the efflorescence and lymphadenopathy, were cardiac enlargement and auricular fibrillation (Case 1), splenomegaly (Case 5), alopecia (Cases 7 and 8), and enlargement of the testicle (Case 10).

There was spontaneous involution of the plaques of mycosis fungoides in Case 5 and of the tumors in Case 3, a remarkable occurrence which, among all the lymphoblastomas, is peculiar to mycosis fungoides. New lesions recurred, as might be anticipated. In several recorded instances, disappearance of the lesions of mycosis fungoides has followed intercurrent infections such as erysipelas or pneumonia.[17] Hyperpyrexia was probably the important factor in these patients, and induced fever has been utilized as a therapeutic measure with some success in recent years.[18]

Laboratory Examinations: Repeated and careful examination of the blood in these 10 patients did not show a typical blood picture to be associated with mycosis fungoides, although a moderate to marked eosinophilia occurred in Cases 1, 3, 5, and 8, and circulating neoplastic cells were encountered in Cases 5 and 9. The sedimentation rate was moderately elevated in Cases 1 and 7.

Bone marrow obtained at autopsy showed evidence of the disease in five patients (Cases 1, 3, 4, 5, and 9), emphasizing the desirability of antemortem bone-marrow studies in mycosis fungoides.

Several of the 10 patients had significant roentgenological findings, shown at necropsy to have been part of the lymphoblastoma (the heart in Case 1, the lungs in Cases 5 and 6), but none of which were of help in establishing the antemortem diagnosis. Changes shown in roentgenograms suggestive of mycosis fungoides involving pulmonary structures have been described,[19] but it is certain that in these instances the roentgenological findings, in the absence of cutaneous lesions of mycosis fungoides, would not have enabled a positive diagnosis to be made. Osseous lesions of mycosis fungoides, demonstrable by roentgenogram, have not been reported.

Pathology: Mycosis fungoides has been regarded as almost exclusively a cutaneous disease for many years, yet involvement of structures and organs other than the skin occurred in eight of the 10 patients. Involvement of various lymph nodes was found in seven of the 10, of the bone marrow in five, the spleen in four, the heart in two, the lungs in two, the kidneys in two, and the liver in two. Other organs or structures involved once among the 10 patients were the appendix, adrenals, dura mater, aorta, diaphragm, breasts, tongue, testes, urinary bladder, pancreas, tonsils, salivary glands, and thyroid gland. Some of the varied clinical manifestations induced by mycosis fungoides in the 10 patients have previously been enumerated, and the list of organs and structures found to be involved at

17. Sequeira.[3] MacCormac, T.: Erysipelas and Mycosis Fungoides, Brit. J. Dermat. **45**:237 (June) 1933.

18. Klauder, J. V.: Fever Therapy of Mycosis Fungoides, J. A. M. A. **106**:201 (Jan. 18) 1936.

19. (*a*) Post and Lincoln.[16] (*b*) Werth, J.: Über Lungenröntgenbefunde bei Mycosis fungoides, Arch. Dermat. u. Syph. **181**:299, 1940. (*c*) Fortnoy, B.: Mycosis Fungoides d'emblee, Lancet **2**:1015 (Oct. 30) 1937. (*d*) Winer, L. H.: Mycosis Fungoides: Benign and Malignant Reticulum Cell Dysplasia, Arch. Dermat. & Syph. **56**:480 (Oct.) 1947.

necropsy emphasizes further the manifold clinical potentialities of this disorder. Findings indicate clearly that mycosis fungoides is a disease to be reckoned with by physicians in all branches of medicine and not a strictly dermatological disorder as maintained for so many years.

The microscopic pathology varied remarkably among the 10 patients. Lesions from which specimens were removed included erythematous patches, premycotic lesions, infiltrated plaques, and nodules and tumors. Nonspecific epidermal alterations were found in several, including parakeratosis, edema, dissolution of the basal layer, and invasion of the epidermis by components of the dermal infiltrate. Pautrier abscesses [20] were not encountered. The dermal infiltrate, however, was the diagnostic kernel of each lesion. In most instances this infiltrate was arranged in bandlike fashion, occupying the papillary and subpapillary portions of the dermis, but in some it extended downward about blood vessels and appendages and in others involved the entire corium. There was vascular dilatation in some specimens, but no abnormal cells were found among the contents of the vessels. Reticuloendothelial cells were the fundamental and outstanding component of the infiltrate in all except Case 10. In addition to reticuloendothelial cells, the infiltrate contained eosinophils in three patients (Cases 2, 3, and 7), lymphocytes in four (Cases 2, 3, 4, and 5), connective-tissue cells in one (Case 3), and lymphoblasts in three (Cases 6, 7, and 10). The occurrence of abundant eosinophils in the premycotic lesions of mycosis fungoides has been emphasized,[21] and some investigators believe that the number of tissue eosinophils bears an inverse relation to the malignancy of the disease.[19d] Eosinophils contribute heavily to the microscopic resemblance which has been noted between eosinophilic granuloma and mycosis fungoides.[22] Clumping of reticuloendothelial cells to form pseudo-giant-cells occurred in Case 4, and a huge number of plasma cells was found in Case 10. There was multiplicity of cell types, described as characteristic of the premycotic and plaque stages of mycosis fungoides,[23] in only two cases (Cases 2 and 3), yet biopsy specimens were removed from premycotic patches and infiltrated plaques in eight patients. Spontaneous resolution of the plaques and tumors of mycosis fungoides occurs when the infiltrate is absorbed and if there is not extensive ulceration; this may occur without fibrosis.[24] It is worth noting, especially from a diagnostic standpoint, that four successive biopsies from various cutaneous lesions failed to substantiate the clinical diagnosis of mycosis fungoides in Case 8 and that only two of six specimens of skin removed at autopsy showed conclusive microscopic evidence of lymphoblastoma.

Tissues and organs removed at autopsy revealed microscopic alterations which differed considerably in several instances compared with changes encountered in biopsies of skin from the identical patients. The neoplasm as it involved the myocardium, lungs, lymph nodes, liver, bone marrow, and spleen in Case 1, a classic example of mycosis fungoides from a clinical standpoint, was found to be

20. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949.

21. Jaffee, R. H., in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1939.

22. Weidman, F. D., in discussion on Winer.[19d]

23. Ormsby and Montgomery.[10] Weiner.[19d] Lever.[20]

24. MacLeod, J. M. H., and Muende, I.: Practical Handbook of the Pathology of the Skin, ed. 3, New York, Paul B. Hoeber, Inc., 1946.

composed of giant cells of the Reed-Sternberg type, reticuloendothelial cells, lymphocytes, plasma cells, and eosinophils. In addition, there were areas of necrosis in some of the lymph nodes and a microscopic picture entirely compatible with a diagnosis of Hodgkin's disease, while observations made on the specimen removed from a mushroom-like tumor five months previously had permitted only the diagnosis of lymphoblastoma. Skin specimens obtained at necropsy in Case 3 contained giant cells which approximated Reed-Sternberg cells closely, in addition to reticulo-

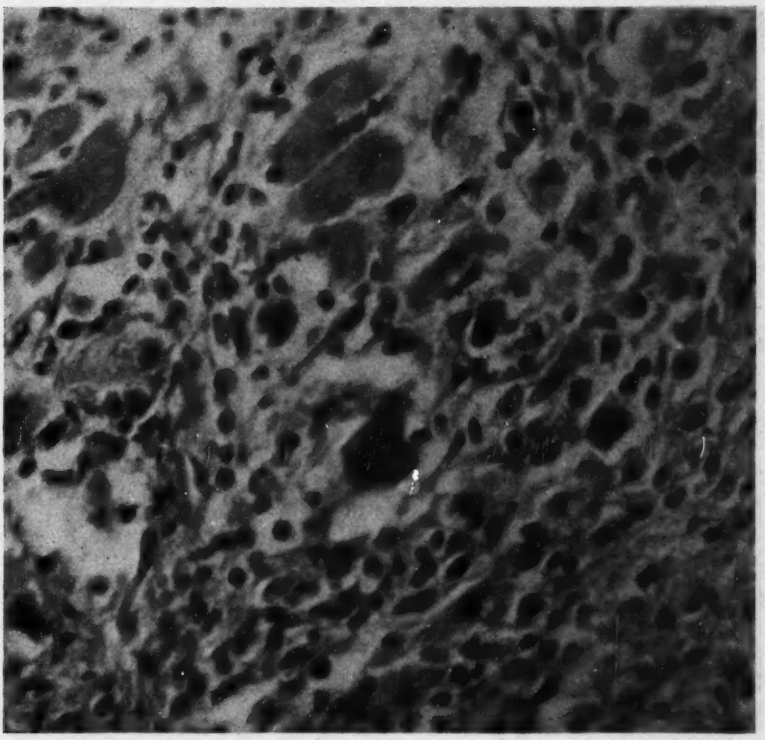

Fig. 2.—Extensive lymphoblastomatous infiltration of the myocardium as it occurred in Case 1. A Reed-Sternberg cell is seen in the center of the field. High power.

endothelial cells, lymphocytes, and fibroblasts, while in the spleen, lymph nodes, and bone marrow the neoplasm was chiefly composed of reticuloendothelial cells with a scattering of large, multinucleated Reed-Sternberg cells. The entire picture was in decided contrast to the previously described cellular architecture of the biopsy specimen, in which eosinophils were abundant and Reed-Sternberg cells absent. The cutaneous infiltrate in the biopsy of Case 4 was composed chiefly of reticuloendothelial cells, some of which had clumped to form pseudo-giant-cells. At autopsy, 16 mo. later, the neoplastic cells in the skin, bone marrow, lymph nodes, aorta, kidneys, adrenals, and dura mater were found to be immature lymphocytes. At

necropsy, eosinophils and lymphoblasts made up the lymphoblastoma in Case 5, while the biopsy previously removed showed reticuloendothelial-cell proliferation and lymphocytic infiltration. In Case 7 microscopic study of the biopsy revealed lymphoblasts, reticuloendothelial cells, and eosinophils, while at autopsy the lymphoblasts and eosinophils had disappeared completely. Lymphoblasts and large numbers of plasma cells were a consistent feature of the microscopic pathology of Case 10, but in addition giant cells of the Reed-Sternberg type, indistinguishable from those

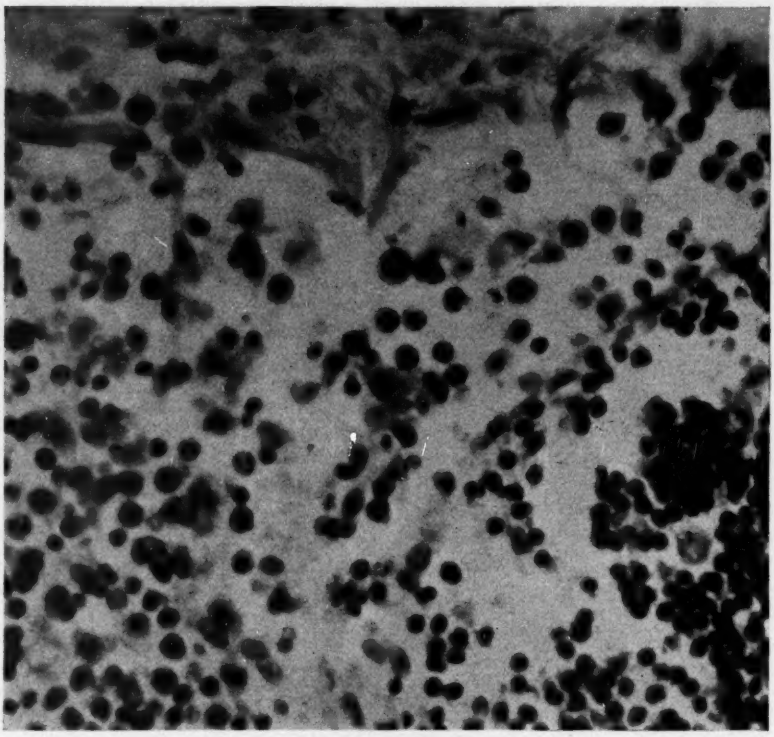

Fig. 3.—One of many lymphoblastomatous focuses in a retroperitoneal lymph node of Case 6. The capsule was involved, as seen in the upper part of the illustration. High power.

which occur in Hodgkin's disease, were found in the lymph nodes at necropsy. The 10 cases, unequivocal clinical examples of mycosis fungoides, may be assembled in the final analysis, and despite occasional discrepancies, into the following pathological groups: Cases 1 (Fig. 2), 2 and 10 (Fig. 3) were examples of Hodgkin's disease, with such an abundance of plasma cells (known to occur at times with Hodgkin's disease [25]) in Case 10 that a diagnosis of plasmocytoma might have been

25. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's Disease and Allied Disorders, New York, Oxford University Press, 1947.

considered. Cases 3, 7, and 9 were found to be lymphoblastomas of reticulo-endothelial-cell type. Cases 4 (Fig. 4), 5, and 6 (Fig. 5) were examples of lymphoblastoma characterized by a preponderance of lymphoblasts, but they did not fit satisfactorily into the category of either lymphosarcoma or leukemia, with the possible exception of Case 5 in which circulating neoplastic lymphoid cells were found on one occasion and one skin biopsy was reported as showing leukemia cutis.

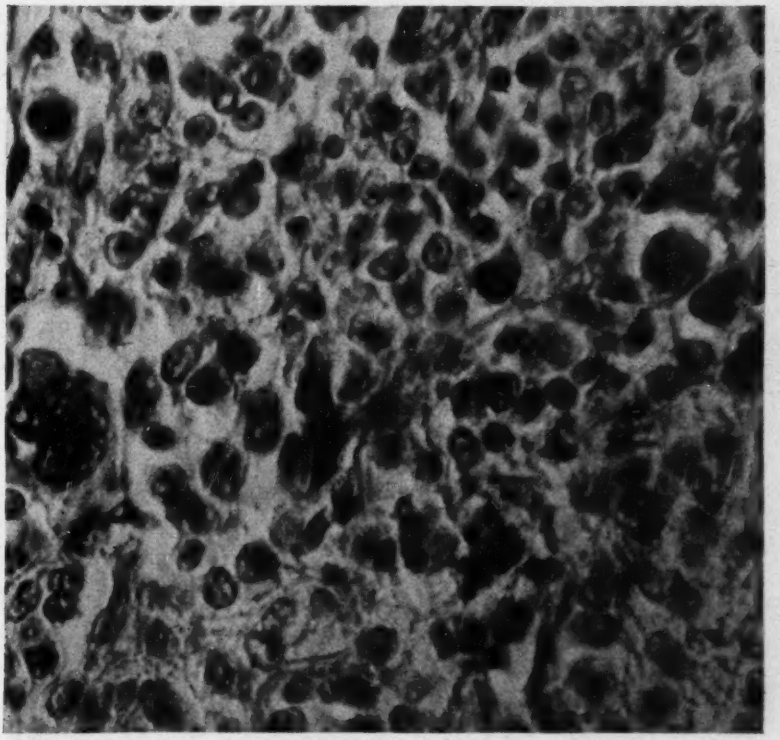

Fig. 4.—Reed-Sternberg cells in a lymph node of Case 10. High power.

Case 8 (Fig. 6) showed at necropsy the multiplicity of cell types in the cutaneous infiltrate which is described as characteristic of mycosis fungoides.

The pathological findings in these 10 cases clearly uphold the alleged reticulo-endothelial origin of mycosis fungoides and its classification among the lymphoblastomas but militate against its recognition as a pathological entity.

Duration of the Disease and Outcome of Patients with Mycosis Fungoides: Among the 10, one patient lived only 13 mo. after the diagnosis of mycosis fungoides was established (Case 3), while another lived 14 yr. (Case 5). The average duration of life was five and three-tenths years after establishment of the diagnosis.

Patients with the disease occasionally live for as long as 35 yr.,[26] but the usual duration is three to six years. The verification of vague and elusive references in the literature to reputedly cured cases of mycosis fungoides is practically impossible, and it is safe to assert that the eventual outcome in cases of mycosis fungoides is almost invariably fatal. Death resulted from cachexia in five patients (Cases 3, 4, 6, 7, and 9), lymphoblastomatous involvement of structures and organs other than the skin in four (Cases 1, 2, 5, and 10), and intercurrent infection in one (pneumonia, Case 8). Information pertaining to the cause of death in mycosis fungoides is difficult to extract from the literature. It appears, however, that damage resulting from excessive x-ray therapy has been a factor in some instances [27] in addition to the causes enumerated above.

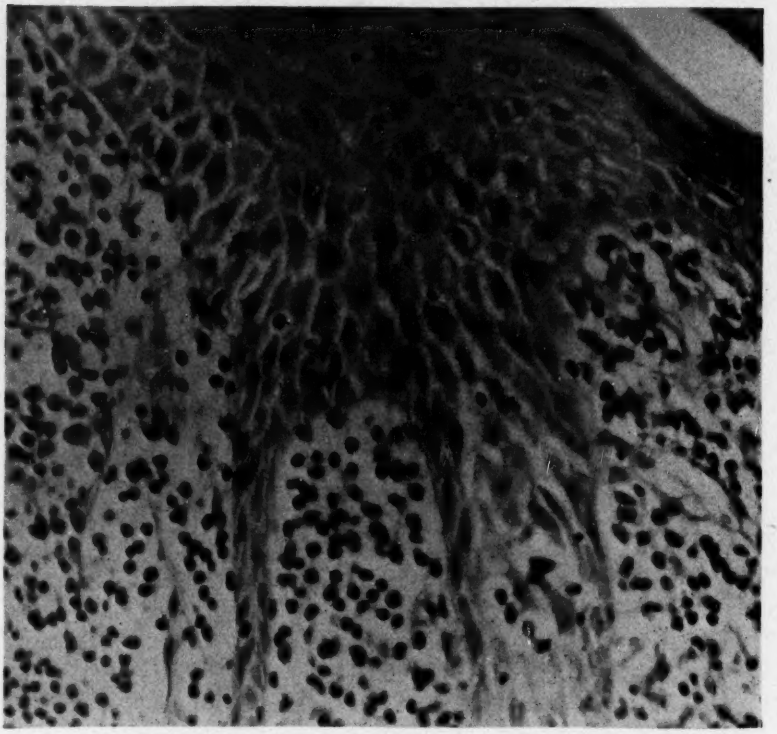

Fig. 5.—A specimen of skin removed at necropsy in Case 4. The infiltrate is composed chiefly of immature lymphocytes. High power.

26. Taylor, G. G. S.: A Case of Mycosis Fungoides Successfully Treated by the X-rays, Lancet **1**:828 (March 17) 1906.

27. Jordan, A., and Areschewa, W.: Das Schicksal der Kranken mit Mycosis fungoides, Dermat. Ztschr. **74**:126 (Oct.) 1936.

Diagnosis: The distinctive clinical features of mycosis fungoides were well established among most of the 10 patients at the time of admission to the hospital and in most instances were the original cornerstone on which the diagnosis was made. Pruritus was a prominent feature in most of the cases and this emphasizes that the occurrence of pruritus with any chronic, ambiguous eruption which is resistant to treatment should direct suspicion toward mycosis fungoides.[28] Diseases simulated at one time or another ran the usual gamut which has already been

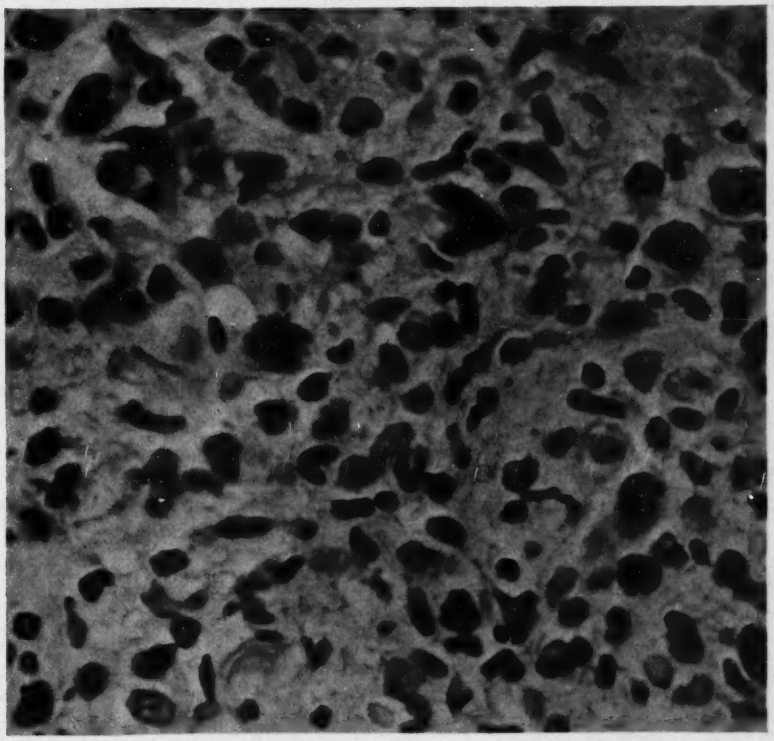

Fig. 6.—The multiplicity of cell types of Case 8 which occurred in a cutaneous specimen removed at necropsy is well shown. High power.

described. The original microscopic observations alone would have established a diagnosis of mycosis fungoides in only two instances (Cases 2 and 3), although the same observations were commensurate with the diagnosis of lymphoblastoma in nine of the 10 patients. As illustrated by these 10 patients, the microscopic features of both cutaneous and visceral mycosis fungoides are inconsistent and vary according to the age, site, and general character of the lesion examined and are also influenced by therapy of various sorts. In conjunction with typical clinical

28. Besnier, E., cited by Portnoy.[19c]

features, however, microscopic observations abet the diagnosis of mycosis fungoides if they can simply be interpreted as those of lymphoblastoma, since mycosis fungoides is a clinical but not a pathological entity among the lymphoblastomas. Other laboratory studies as they apply to the diagnosis of mycosis fungoides have already been discussed.

Treatment: The protracted list of medications and therapeutic agents employed in the treatment of mycosis fungoides is mute testimony as to their inefficacy. The compounds which include urethan, the nitrogen mustards, and folic acid antagonists hold some promise, but on the basis of previously attained results x-ray therapy continues to be the treatment of choice.

SUMMARY

1. This paper is based on a review of the cases of 10 patients studied at the Dermatology Service of the University Hospital whose disease was diagnosed as mycosis fungoides and who were subsequently examined at necropsy and is concerned with the nosology of mycosis fungoides and some of its clinical and laboratory features which have remained obscure.

2. The family history was notable in one case because the patient's mother had also died of mycosis fungoides and in another because of the occurrence of two cases of leukemia and one of pernicious anemia in the patient's family.

3. Vesicular and bullous mycosis fungoides, as occurred in one of the 10 patients, is exceedingly rare, and involvement of oral mucous membranes, the original manifestation of the disease in another patient, is also distinctly uncommon, although the latter point has been little emphasized. Spontaneous involution of plaques and tumors, a remarkable occurrence, took place in two of the 10.

4. Nearly all examples of mature mycosis fungoides, as among these 10, present a conglomeration of cutaneous lesions, and the three stages of the disease comprise artificial subdivisions which frequently do not present themselves in orderly sequence.

5. Repeated and careful examination of the blood in these 10 patients did not show a typical blood picture to be associated with mycosis fungoides, although a moderate to marked eosinophilia occurred in several. Bone marrow obtained at autopsy showed evidence of the disease in five, emphasizing the desirability of antemortem bone-marrow studies in mycosis fungoides. Three of the 10 patients had significant roentgenological findings, shown at autopsy to have been caused by the lymphoblastoma (enlarged heart, pulmonary changes) but none which were of positive assistance in establishing the diagnosis.

6. Mycosis fungoides has been regarded as almost exclusively a cutaneous disease for many years, yet involvement of structures and organs other than the skin occurred in eight of the 10 patients, indicating clearly that mycosis fungoides is a disease to be reckoned with by physicians in all branches of medicine and not a strictly dermatological disorder, as formerly maintained.

7. Structures and organs found to be involved, other than the skin, were various lymph nodes in seven of the 10 patients, the bone marrow in five, the spleen in four, the heart in two, the lungs in two, the kidneys in two, and the liver in two. Other organs or structures involved once among the 10 patients were the appendix,

adrenals, dura mater, aorta, diaphragm, breasts, tongue, testis, urinary bladder, pancreas, tonsils, salivary glands, and thyroid gland.

8. The average duration of life among these patients was five and three-tenths years after the diagnosis of mycosis fungoides was established. The causes of death were cachexia, lymphoblastomatous involvement of structures and organs other than the skin, and intercurrent infection.

9. The microscopic pathology varied remarkably among these 10 patients with mycosis fungoides. The dermal infiltrate was the diagnostic kernel of each cutaneous lesion, and reticuloendothelial cells were the fundamental component of the dermal infiltrate in nine of the 10.

The original cutaneous microscopic observations alone would have established a diagnosis of mycosis fungoides, based on alterations described as characteristic of the disease, in only two instances, although these same observations were commensurate with the diagnosis of lymphoblastoma in nine of the 10 patients. The microscopic features of both cutaneous and visceral mycosis fungoides are inconsistent and vary according to the age, site, and general character of the lesion examined and are also influenced by therapy of various sorts.

The 10 cases can be assembled in the final analysis into the following pathological groups: three examples of Hodgkin's disease, three of lymphoblastoma of reticuloendothelial-cell type, three of lymphoblastoma characterized by a preponderance of lymphoblasts but not fitting satisfactorily into the category of either lymphosarcoma or leukemia, and one which showed the polymorphous cutaneous infiltrate which is described as characteristic of mycosis fungoides.

10. The over-all findings in these 10 cases clearly uphold the alleged reticuloendothelial origin of mycosis fungoides, its classification among the lymphoblastomas, and its acceptance as a clinical entity but militate against its recognition as a pathological entity.

ABSTRACT OF DISCUSSION

DR. RICHARD S. WEISS, St. Louis: I shall start out by admitting that in preparing this opening discussion I felt a sense of inadequacy and so I sought help. Therefore these remarks are a joint presentation of Dr. Zola Cooper and me.

The authors are to be congratulated on such a large series of cases with the results of complete autopsies. Berman (Pathologic Nature of Mycosis Fungoides, *Arch. Path.* **29**:530-540 [April] 1940) collected 60 cases from the literature for the period 1928 to 1938. Of these, 42 were reported without autopsy findings and only 18 with complete autopsy findings. In 16 of these 18 cases the internal organs were involved. This contribution is well worth reading and emphasizes the relations between the various members of the lymphoblastoma group.

We agree that mycosis fungoides is a lymphoblastoma, and that it is not a strictly cutaneous disorder. We should like to emphasize that more recent work is tending to show that none of the lymphoblastomas are definite entities throughout their course, and that transitions from one to another seem to be the rule rather than the exception. We should like to call attention to the work of Custer and Bernhard who reported autopsy and biopsy observations from 700 cases of Hodgkin's disease and 600 cases of other lymphomas (follicular lymphoblastoma, lymphosarcoma, reticular-cell sarcoma, lymphatic leukemia, and monocytic leukemia. Of the cases of Hodgkin's disease 138 included one, two, or three antemortem biopsy observations, plus the results of complete autopsies. From this material they constructed the chart.

Custer's chart would seem to be fairly conclusive evidence that the lymphoblastomas are not hard and fast entities. My pathology department (Washington University School of Medicine) now diagnoses such diseases as malignant lymphoma of Hodgkin's type and reticular cells of the sarcoma or undetermined type. Mycosis fungoides shows this same fluidity in its histological

pattern but is as much of an entity as the others. It is quite conceivable that some lymphoblastomas arise in the skin.

In normal skin, about blood vessels and lymphatics there are always some histiocytes. These cells are derived from the reticuloendothelial system. MacLeod and Muende in "Pathology of the Skin" point out that there may be a connection between these cells and the pathological group of diseases to which mycosis fungoides, cutaneous Hodgkin's disease, and leukemia belong. It is conceivable that mycosis fungoides, as well as some of the other lymphoblastomas, may have its origin in the skin rather than in the bone marrow. This would help to explain the normal blood pictures existing over a period of years after the skin lesions have become evident. If mycosis fungoides has its origin in the skin, the long duration of the disease before visceral lesions become evident would also be more understandable.

Let me close by quoting from the paper by Custer and Bernhard (The Interrelationship of Hodgkin's Disease and other Lymphatic Tumors, *Am. J. M. Sc.* **216**:625-641 [Dec.] 1948). "Analysis of 1,300 lymphatic tumors, many sampled several times during their progress, showed a striking fluidity in histologic pattern, with transitions and combinations that could best be interpreted as indicating a single neoplastic entity having a number of variants."

Therefore from the pathological standpoint Dr. Cawley, Dr. Curtis, and Dr. Leach have confirmed the above-quoted work, and from the clinical standpoint their studies confirm what most dermatologists have suspected for many years.

DR. JAMES H. MITCHELL, Chicago: It may be of some interest to you to know that we have had two patients with mycosis fungoides hospitalized in the Presbyterian Hospital, and both have been treated intensively under the care and management of Dr. Samuel Taylor and Dr. Morris, who presented the paper the morning of June 28, 1950 on the steroids. One patient was under my care for a number of years and was given everything possible in the way of treatment.

Dr. Curtis had suggested at one time that we give both patients sodium paraaminobenzoic acid. One did better with this than with any other treatment up to the time of the late stages. This patient was also given antimony potassium tartrate injections and various other medication and finally a number of doses of nitrogen mustard. Dr. Straus, who had charge of the nitrogen mustard, when asked if I should give her another, replied that the consequences might be fatal. With the best kind of care, ACTH (adrenocoticotropic hormone) was administered with very careful chemical studies. Despite this intensive treatment, the patient died recently.

Another patient came into the hospital in January, who had had mycosis fungoides for 16 yr. This patient was likewise given the same care by Dr. Taylor and his associates; however, no effect at all was observed.

My information is that these are the first two patients to have been treated with ACTH, and I must report failure in both.

DR. DUDLEY SMITH, Charlottesville, Va.: We all know, of course, that mycosis fungoides is a very variable condition from a gross clinical viewpoint. This variation and great change in the cellular element is true not only in the cellular changes in the skin itself, but also in the blood findings and in the bone-marrow changes.

My only purpose in getting up is to say that, in the May 1950 issue of the *Journal of Investigative Dermatology*, Dr. Tilley and I reported, in detail, our findings on bone marrow in patients with mycosis fungoides. We were unable to confirm the conclusion by some that in this disease there is a reticuloendothelial type of reaction. There were no changes in the bone marrow that were consistent all the way through. Eosinophila was present in some, absent in some. Certain types of lymphocytic cells were present in some and absent in some. There was nothing that was true always in all the patients. That may have some implications. Is mycosis fungoides a single entity or is it a group of diseases?

DR. EDWARD P. CAWLEY, Ann Arbor, Mich.: So far as we have been able to determine, there are no mutations among the various lymphoblastomas. We believe that mycosis fungoides is simply a clinical entity and not a pathological one.

RISE AND GROWTH OF DERMATOLOGY IN NEW YORK

PAUL E. BECHET, M.D.
ELIZABETH, N. J.

The historian's aim should be to collect with judgement and at the same time write with spirit.—William M. Sloane, Professor of History, Princeton University, 1883-1896; Seth Low Professor of History, Columbia University, 1896-1916.

I BELIEVE that this is the first time that a symposium on the history of dermatology has ever been presented before a medical body. That the Committee on Education of such an important organization as our American Academy of Dermatology and Syphilology decided to present this symposium evidences the growing interest in the history of our specialty and their appreciation of the immense amount of groundwork done by our dermatological forebears, as also the importance of their superlative contributions to the specialty we so greatly love.

In order to allay any qualms of jealousy amidst many personal friends living in cities equally important to those mentioned, may I state that it is my impression that the cities of New York, Philadelphia, Boston, and Chicago were designated for this symposium simply because they are the centers of an immense population, and the rapid development of the specialty of dermatology in them was not due to any special group of supermen, but rather to the very primitive law of supply and demand; the larger the population, the greater are its dermatological ills, and the demand for experts to relieve these ills is consequently so great as to stimulate and activate the study of dermatology to an unusual degree, and this is especially true in America's largest city, New York. The above statement is made lest the relation of the great number of dermatological "firsts" in New York overstimulate the ego of the younger generation of dermatologists residing in that city.

To go into the complete details of the rise and growth of dermatology in New York and its share in the progress of the specialty in America and include all of the men responsible for it would take hours to relate, so that this recital must restrict itself to the more important contributions of the "stars" of the dermatological stage in New York.

American dermatology began in New York on June 22, 1836, when the Broome Street Infirmary for Diseases of the Skin was opened under the direction of Henry Daggett Bulkley.[1] One year later he instituted a series of lectures on cutaneous diseases at the Broome Street Infirmary, and he continued these lectures during the next three years at the Broome Street School of Medicine, at the New York Dispensary, and later at the College of Physicians and Surgeons, then located on

Read in a symposium on History of Dermatology at the Ninth Annual Meeting of the American Academy of Dermatology and Syphilology, Chicago, Dec. 7, 1950.

1. Bechet, P. E.: Early History of American Dermatology, Arch. Dermat. & Syph. **45**:482 (March) 1942.

Crosby St., delivering nine courses of lectures here during the following 10 years. Bulkley was therefore not only the first to lecture on dermatology in America but the first to practice the specialty exclusively in America. He was born in New Haven, Conn., on April 4, 1804. He received an academic degree from Yale College in 1821. He studied medicine at Yale and graduated in 1830. After graduation he went to Paris, in 1831, where he became the first American dermatological student under Biett and Cazenave, at the old Hôpital Saint-Louis. He translated into English the "Manual of Diseases of the Skin," by Cazenave and Schedel, in 1845 and in 1851 edited an American edition of Gregory's "Eruptive Fevers." At different times he was president of the New York Academy of Medicine and the New York County and New York State Medical Societies. It was at his home at 42 E. 22d St. that the New York Dermatological Society was founded, and he was its first president. He died of pneumonia on Jan. 4, 1872, in his 68th year.

The New York Dermatological Society is the oldest dermatological society in the world and was founded on May 18, 1869.

This historic occasion was due to the efforts of Dr. Faneuil D. Weisse, who conceived the idea of a dermatological society in America while studying his specialty abroad. A letter was sent to certain physicians interested in dermatology, signed by Drs. Faneuil D. Weisse, H. D. Bulkley, Henry G. Piffard, and Foster Swift, reading:

> Knowing as we do that you are interested in dermatology, we would wish you to participate with us in the organization of a society to be devoted to the investigation and consideration of the same. The object of the New York Dermatological Society shall be to afford all those interested in this most important department of medicine an opportunity for a full exchange of their opinions and methods of practice, and to contribute American experience and investigations to the fast accumulating stock of our knowledge of diseases of the skin.

Ten men responded in the affirmative to this letter and in so doing helped to launch a society which in 81 years has never missed its eight monthly meetings a year. Its popularity is attested by the fact that the complete roster of members from 1869 to date numbers 88, and 72 remained members until their death. George H. Fox once told me that a devoted member of the society passed the remark that in 20 years no member had resigned, or even died, thus evidencing that the joys of membership were sufficiently great even to defeat the old gentleman with the hourglass and scythe.

In 1870, a year after the founding of the New York Dermatological Society, the first journal on dermatology in America made its appearance in New York under the editorship of M. H. Henry, a New Yorker. It was entitled *The American Journal of Syphilology and Dermatology*, and under different titles but without interruption it has appeared ever since. In its span of 80 years it has proved invaluable to American dermatologists, and its appearance caused a tremendous increase in dermatological activity throughout the country.

The years 1841 through 1846 proved exceedingly generous to our specialty in New York, for they gave birth, in chronological order, to a constellation of brilliant men, in the persons of Samuel Sherwell, Henry G. Piffard, Robert W. Taylor, Edward L. Keyes, Andrew R. Robinson, L. Duncan Bulkley, George H. Fox, and Prince A. Morrow.

Samuel Sherwell was the first teacher of dermatology at the Long Island Medical College (1877) and first to practice this specialty in Brooklyn, where he remained active for some 55 years. He received his medical degree from University and Bellevue Medical College in 1868 and did postgraduate work in Europe until the outbreak of the Franco-Prussian war in 1870, when he served in the Anglo-American Ambulance Corps with Sir William McCormack and Marion Sims. For these services he received from the Bavarian government the military order *Pour le mérite*. He was elected president of the New York Dermatological Society in 1881 and again in 1909. He was also president of the American Dermatological Association in 1894. He wrote a number of dermatological articles, the most outstanding of which was on his use of acid nitrate of mercury after thorough curettage in the treatment of epitheliomas of the skin, a method which proved highly efficacious, giving at the same time excellent cosmetic results. Sherwell died in 1928, at the age of 87, after an eventful and interesting life. His "Recollections of an Old Boy" [2] makes fascinating reading.

Henry G. Piffard,[3] the author of the second American textbook on dermatology, graduated in medicine from the College of Physicians and Surgeons in 1864, and he studied dermatology abroad, spending most of his time at the University College Hospital in the dermatological clinic of Tilbury Fox. On his return to New York he rose so rapidly that within a few years he attained such dermatological eminence that he helped to found the New York Dermatological Society and the American Dermatological Association and received in 1871 an appointment as visiting dermatologist to the New York City Hospital (Welfare Island), which was the first institution in the United States to establish dermatological wards as early as 1866, when Dr. Freeman J. Bumstead received the first appointment as visiting dermatologist.[4] Piffard was a great teacher and as early as 1874 became professor of diseases of the skin at New York University, and in 1875 he started postgraduate instruction, which he kept up after 1882 at the New York Post-Graduate Medical School and Hospital.[5] Piffard also wrote the first American textbook on dermatotherapy in 1881,[6] but as early as 1868 he had published a translation of Hardy's "The Dartrous Diathesis or Eczema and Allied Affections." In collaboration with G. H. Fox he published in 1877 a small book for the use of students, which is now very scarce.[7] Piffard was a dynamo of energy, a genial fighter, avid hobbyist, profound thinker, and forceful teacher. He died of pneumonia on June 8, 1910, at the age of 68. As his life-long friend, George Henry Fox, aptly put it, he was "a blazing meteor in our dermatologic firmament."

Robert M. Taylor received his medical degree from the College of Physicians and Surgeons in 1868. He first described idiopathic progressive atrophy of the

2. Sherwell, S.: Recollections of an Old Boy, New York, Knickerbocker Press, 1923.

3. Piffard, H. G.: An Elementary Treatise on Diseases of the Skin, for the Use of Students and Practitioners, New York, Macmillan & Co., 1876.

4. Bechet, P. E.: City Hospital: History of Its Dermatological Division, Arch. Dermat. & Syph. **39**:674 (April) 1939.

5. Bechet, P. E.: Skin and Cancer Unit of New York Post-Graduate Medical School and Hospital, Columbia University: Historical Review, Arch. Dermat. & Syph. **42**:117 (July) 1940.

6. Piffard, H. G.: A Treatise on the Materia Medica and Therapeutics of the Skin, New York, William Wood & Company, 1881.

7. Piffard, H. G., and Fox, G. H.: Cutaneous and Venereal Memoranda, New York, William Wood & Company, 1877.

skin in 1876.[8] In 1875 he wrote "Syphilitic Lesions of the Osseous System in Infants and Young Children,"[9] a pioneer and most important contribution to the study of bone syphilis. He published a large folio on venereal and skin diseases in 1889. He was the first to teach dermatology at the University of Vermont and succeeded George Henry Fox as professor of dermatology at the New York Post-Graduate Medical School and Hospital. Taylor was a founder of the American Dermatological Association and its president in 1882. He was president four times of the New York Dermatological Society. He died in 1908 at the age of 66.

Edward L. Keyes graduated from New York University Medical College in 1866. On the advice of his preceptor, William H. Van Buren, he went abroad to specialize in dermatology. In 1871 he was appointed lecturer in dermatology at Bellevue Hospital Medical College, and in 1881, professor of cutaneous and genito-urinary diseases at the same school. Keyes was deeply interested in genitourinary surgery, but he made a number of valuable contributions to dermatology, among which may be mentioned the invention of the cutaneous punch for biopsies. One of his greatest contributions was a paper on the tonic effect of small doses of mercury on syphilitic blood, which first appeared in January, 1876.[10] This paper was incorporated in an essay on the same subject which was read by Keyes before the Section on Dermatology and Syphilis at the International Medical Congress at Philadelphia in September, 1876. Keyes was a charter member of both the New York Dermatological Society and the American Dermatological Association. Van Buren and Keyes collaborated on a textbook on genitourinary diseases which remained a classic for many years.

Andrew Rose Robinson graduated in medicine at Bellevue Hospital Medical College in 1868 and the University of Toronto in 1869. He did postgraduate work in dermatology in London, Paris, and Vienna, where he became especially interested in histopathology; this interest led to his appointment as professor of histology and pathologic anatomy at the New York University Medical College and Women's Medical College of the New York Infirmary for Women and Children. He can therefore be considered the pioneer histopathologist in America. But the institution nearest his heart was the New York Polyclinic Medical School and Hospital, of which he was one of the founders and professor of dermatology for many years. He wrote a "Manual of Dermatology" and was the first to describe hydrocystoma.[11] Robinson served as president of the Section of Dermatology and Syphilology at the Ninth International Medical Congress in 1887 and of the American Dermatological Association in 1896. He was the first chairman of the Section of Dermatology and Syphilology of the New York Academy of Medicine.

On Jan. 1, 1883, the doors of a small house at 243 E. 34th St. were opened to patients with skin diseases, and that act marked the beginning of not only the first hospital in New York devoted to dermatology but also the largest of such kind in America, a position it has maintained ever since.[12] On the staff of the New York

8. Taylor, R. M.: Arch. Dermat. **2**:114, 1876.

9. Taylor, R. M.: Syphilitic Lesions of the Osseous System in Infants and Young Children, New York, William Wood & Company, 1875.

10. Keyes, E. L.: Am. J. M. Sc. **71**:17, 1876.

11. Robinson, A. R.: J. Cutan. Dis. **2**:362, 1884; **11**:293, 1893.

12. Bechet, P. E.: M. J. & Rec. **138**:440, 1933.

Skin and Cancer Hospital many of the representative dermatologists of New York have served at different times. Even in 1883, its first year, one may find on its consulting staff such famous New York names as William H. Draper, Fordyce Barker, T. Gaillard Thomas, Edward G. Janeway, Alfred L. Loomis, and Abraham Jacobi. An outstanding member of the group which founded the hospital and the one most responsible for its existence was Dr. L. Duncan Bulkley; it was he who conceived the original idea. He was the son of Henry Daggett Bulkley. L. Duncan Bulkley graduated in medicine from the College of Physicians and Surgeons in 1869, studied dermatology at the Hôpital Saint-Louis, and on his return to New York became most active in dermatology. His monograph "Syphilis in the Innocent" [13] won the Alvarenga prize in 1891 from the College of Physicians of Philadelphia. He wrote several hundred articles and six or eight textbooks, mostly devoted to dermatotherapy, in which he had a deep interest. He was one of the founders of the American Dermatological Association and secretary of its first annual meeting, which was held in Niagara Falls, N. Y., on Sept. 4, 1877. L. Duncan Bulkley was also one of the founders of the Section on Dermatology and Syphilology of the American Medical Association and chairman at its first meeting, on May 8, 1888. Bulkley died in 1928 at the age of 83.

In 1879 George Henry Fox marked an epoch in the illustration of skin diseases when he published his "Photographic Illustrations of Skin Diseases," the first successful attempt to illustrate dermatoses by means of photography.[14] He also published "Skin Diseases in Children" (1897)[15] and his "Reminiscences" (1926).[16] He was the first to describe a chronic, itching, papular eruption of the axillae and pubes (Fox-Fordyce disease).[17] The clinical observations were done entirely by him. Fordyce did only the histology. Fox was probably the first to report a contact dermatitis when he described matchbox dermatitis as early as 1888. After receiving his medical degree from the University of Pennsylvania in 1869, he served an internship at "old Blockley," where, by a strange coincidence, he succeeded Louis A. Duhring, of Philadelphia, another great American dermatologist.[18] On the completion of his internship at the Philadelphia (Blockley) Hospital, Fox left for Europe, where for three years he studied dermatology, in Berlin under Virchow, in Vienna under Hebra, Neumann, Schroetter, and Stoerck, in Paris with Bazin, Hardy, and Vidal, and in London under Tilbury Fox and Jonathan Hutchinson.

Fox became a great teacher and served at different times as professor of dermatology, from 1875 to 1907, at the Women's Medical College of the New York Infirmary, Starling Medical College, Columbus, Ohio, the New York Post-Graduate Medical School and Hospital, and the College of Physicians and Surgeons in New York. He resigned from the last institution before the age limit in order to enable his chief assistant, Dr. George T. Jackson, to become full professor before also attaining the age limit. Fox served as president of the Medical Society of the County of New York in 1891 and of the Medical Society of the State of New York

13. Bulkley, L. D.: Syphilis in the Innocent, New York, G. P. Putnam's Sons, 1882.
14. Fox, G. H.: Photographic Illustrations of Skin Diseases, New York, E. B. Treat, 1879.
15. Fox, G. H.: Skin Diseases of Children, New York, William Wood & Company, 1897.
16. Fox, G. H.: Reminiscences, New York, Medical Life Press, 1926.
17. Fox, G. H.: J. Cutan. & Genitour. Dis. **20**:1, 1902.
18. Bechet, P. E.: Louis Adolphus Duhring: Great American Dermatologist, Arch. Dermat. & Syph. **30**:369 (Sept.) 1934.

in 1894. He was president four times of the New York Dermatological Society and a founder (1876), president (1892), and honorary president at its golden anniversary meeting in 1926, of the American Dermatological Association. Most of Fox's clinical work was done at the New York Skin and Cancer Hospital,[12] where he was attending dermatologist from 1883 to 1913. One of the great satisfactions of my life was my close association with Dr. Fox over many years. On the many occasions that we were together, I have never heard him speak of his own honors, but he was always ready to speak of those around him who had attained a high degree of proficiency in the specialty he had so greatly loved. Another of Dr. Fox's most lovable traits was the extraordinary friendships and interest which he manifested for the young tyros of his specialty. His willingness to help them in every way possible was expressed without the slightest trace of condescension. As Pusey rightly stated, "He was perhaps the friend of more American dermatologists than any other one of his generation." Fox died on May 3, 1937, at the age of 91.

Prince A. Morrow was born on Dec. 19, 1846, at Mount Vernon, Christian County, Ky. He received his degree in medicine from New York University in 1873, and after two years of dermatological work in Europe, he located in New York, where he rapidly rose to eminence. He became professor of dermatology and genitourinary diseases at New York University and Bellevue Hospital Medical College in 1883. He was also an attending physician to the department of cutaneous and venereal diseases of the New York Hospital. He was a corresponding or honorary member of most of the foreign dermatological societies, and he served as secretary of the International Congress of Dermatology and Syphilology in Paris in 1890 and in Vienna in 1893. He edited the *Journal of Cutaneous and Genitourinary Diseases* with Piffard from 1883 to 1888 and with Fordyce from 1888 to 1891. He was the author of "Drug Eruptions" (1887), "An Atlas of Skin and Venereal Diseases" (1888-89), "A System of Genitourinary Diseases," Syphilography and Dermatology," three volumes (1892-1894), "Leprosy" (1880), "Social Diseases and Marriage" (1904). Morrow, through Fournier's "Syphilis and Marriage," which he translated into English in 1880, received the inspiration to take up the prophylaxis of syphilis, so that later on in life he practically made it his life's work. He founded the Society of Sanitary and Moral Prophylaxis in 1905 and remained its president until his death in 1913. He was the founder and editor of *Social Diseases*, a journal devoted to venereal prophylaxis.

John A. Fordyce graduated in medicine from Northwestern University Medical School in Chicago in 1881, served as intern in the Cook County Hospital until 1883, practiced general medicine at Hot Springs, Ark., for three years, studied dermatology abroad for two years, and on his return to the United States in 1888 settled in New York. Fordyce served as professor of dermatology and syphilology at New York University School of Medicine from 1893 to 1912, when he resigned in order to accept a similar position at the College of Physicians and Surgeons. He retained this position until his death. He also served the New York City Hospital most faithfully as visiting dermatologist from 1893 until his death in 1925. In 1889 he became co-editor with Prince A. Morrow of the *Journal of Cutaneous and Genitourinary Diseases*. From 1892 on he was its sole editor until his resignation in 1897. Fordyce was a prolific writer, and—what is more important—of his more

than a hundred monographs, many marked an advance in the specialty to which he devoted a superabundant energy. He became at different times the presiding officer of the more important dermatological societies in America. Despite a large practice, extensive teaching, and much hospital and executive work, he always found time to encourage and help the younger physicians, no matter how obscure. Fordyce was a great histopathologist, a bent in this direction having developed under the inspiration of Kaposi. He was also a pioneer in the modern treatment of neurosyphilis. In 1896 he first described pseudocolloid of the lips (Fordyce's disease) under the following title, "A Peculiar Affection of the Mucous Membrane of the Lips and Oral Cavity."[19] "Infectious Eczematoid Dermatitis: Possible Influence of Anaphylaxis in Skin Reactions"[20] appeared in 1911 and probably was one of the earliest expositions of skin eruptions caused by allergy. Like most great men, Fordyce was modest and extremely diffident. American dermatology suffered an irreparable loss in his death, on June 4, 1925, two weeks after an appendectomy.

Sigmund Pollitzer graduated from the College of Physicians and Surgeons in 1884. After graduation he undertook research work in physiology in Heidelberg, Germany, and in bacteriology in Fresenius' laboratory in Weisbaden, Germany; later he took up special work in Virchow's laboratory and at this time did much original work in physiologic chemistry. It was not until 1889 that he entered on his life's work, first at Unna's clinic and then as an assistant to Sir Malcolm Morris, in which position he edited for some time the *British Journal of Dermatology* under Morris' direction. From London he went to Paris and there began a lifelong friendship with Darier, whose textbook he translated into English in 1920. Pollitzer was the first to describe the following dermatoses: acanthosis nigricans,[21] hydradenitis destruens suppurativa,[22] and parakeratosis variegata with Unna and Santi.[23] Pollitzer, in 1910, reported the first case in which rhinoscleroma was cured with X-rays.[24] He did much pioneer work dealing with the modern concept of syphilis. Pollitzer served as vice-president (1913) and president (1914) of the American Dermatological Association and was one of its most active members for 41 years. He was professor of dermatology at the New York Post-Graduate Medical School and Hospital from 1885 to 1915. Pollitzer was a strict parliamentarian and was especially critical of long-winded discussions lacking concrete facts. In such instances he could, in a few words of polished English and in well-chosen scientific terms, completely smother the unhappy speaker with unassailable facts, from which there was nothing else to do than to retire in confusion. Pollitzer, in acting thus, did much good service, for he deflated the ego of the usual group of know-it-alls who frequent every dermatological meeting. In his home and with his friends he exuded kindness, generosity, and simplicity. Pollitzer always evinced much friendship for me; why, I do not know, but it did bring me great happiness. He belongs to that small group of physicians who have placed dermatology on a sound, dignified, and

19. Fordyce, J. A.: J. Cutan. Dis. **14**:413, 1896.

20. Fordyce, J. A.: J. Cutan. Dis. **29**:129, 1911.

21. Pollitzer, S., in International Atlas for Rare Skin Diseases, Leipzig, Leopold Voss, 1891, Plate 10.

22. Pollitzer, S.: J. Cutan. Dis. **10**:9, 1892.

23. Pollitzer, S.: Monatschr. prakt. Dermat. **10**:404, 1890.

24. Pollitzer, S.: J. Cutan. Dis. **28**:338, 1910.

scientific basis. His death in 1937 was a severe blow to those of us who knew him well enough to appreciate his many qualities of mind and heart.

From 1900 the progress of dermatology in New York increased by leaps and bounds. The Manhattan Dermatological Society, the second oldest in New York, was organized on Nov. 21, 1900. The section of Dermatology and Syphilis of the New York Academy of Medicine was authorized by its trustees in 1906, and a number of new dermatological societies have been formed within the past 20 years.

Postgraduate teaching of dermatology began in New York as early as 1875, when a postgraduate faculty was formed at the School of Medicine of New York University, with Dr. Henry G. Piffard in charge of dermatology. This faculty was permitted to grant certificates to physicians completing the course. Their success was so great that by 1881 they realized the inadequacies of the conditions under which they were working and the necessity of a separate building and complete segregation from the undergraduates. The university was not prepared to accede to these just demands, so on April 4, 1882, this group resigned and founded the New York Post-Graduate Medical School, which opened its doors on Nov. 6, 1882, and, in sequence, first under Piffard, then George H. Fox, Robert W. Taylor, George T. Elliot, Sigmund Pollitzer, A. Schuyler Clark, and George M. MacKee, the dermatological teaching became so popular that its facilities were greatly overtaxed. In 1934 the New York Post-Graduate Medical School absorbed the New York Skin and Cancer Hospital, which from its inception in 1882 had always had the largest skin clinic in America. Under Dr. George M. MacKee the entire building of the New York Skin and Cancer Hospital was renovated and altered in order to create a complete, self-contained dermatological unit, where all divergent branches of dermatology, investigative and otherwise, could be studied and cared for under a single roof. Within the past three years New York University and the Post-Graduate Medical School and Hospital and its Skin and Cancer Unit have amalgamated into a single unit, thus greatly increasing the facilities for expert teaching.

The New York Polyclinic Medical School and Hospital has for years maintained a most efficient teaching staff.

Most of the medical schools in New York have within the past 20 years established postgraduate departments in dermatology in which a budding dermatologist can attain the full bloom of an expert, provided he is willing to work diligently.

SUMMARY

It might be well at this time to summarize in chronological order the substantial contributions to American dermatology made by New York men.

1. Henry D. Bulkley (1804-1872), of New York, was the first to practice and teach dermatology in America and the first American student to study his specialty abroad, at the Hôspital Saint-Louis (1831).

2. The New York Dermatological Society was founded in 1869, becoming the first dermatological society in the world.

3. In New York in 1870 was first published *The American Journal of Dermatology and Syphilology*, under the editorship of Dr. M. H. Henry of New York.

4. Samuel Sherwell (1841-1927) was the first dermatologist to practice in Brooklyn and the first teacher of dermatology at the Long Island Medical College (lecturer in 1877 and professor a few years later).

5. New York City Hospital was the first hospital in America to establish dermatological wards (1866).

6. New York University Medical College was the first to give postgraduate instruction in dermatology (1875), under Henry G. Piffard.

7. The New York Skin and Cancer Hospital was the first hospital in New York for the treatment of skin diseases and cancer (1882), under the direction of L. Duncan Bulkley and George H. Fox.

8. Twelve new cutaneous diseases were first identified by New York dermatologists.

9. Of the 16 founders of the American Dermatological Association in 1876, seven were from New York, and of these seven men, three had founded the New York Dermatological Society in 1869.

EPILOGUE

In the difficult early years of dermatology in America, there is no doubt that the pioneer dermatologists of New York played star roles in the development of their specialty in this country. The present enviable position of dermatology in the United States is substantially due to their tremendous ability, capacity for work, and complete unselfishness; but all these prerequisites were of course equally shared by many other American dermatologists; the names of Worcester, White, Hyde, Duhring, Hardaway, Ravogli, Stelwagon, Gilchrist, and Pusey, to name only a few of them, will live forever, and this will be clearly proved by the other essayists in this symposium.

May I, in closing, express the hope that this symposium will bring to resplendent life the small band of devoted, tireless American pioneers in our chosen field of medicine? If it does, I will feel that my effort to achieve this purpose has been amply rewarded.

1364 North Ave.

FERDINAND VON HEBRA

In Commemoration of His Appointment One Hundred Years Ago as Professor of Dermatology at the University of Vienna

ERNEST SPITZER, M.D.
ST. LOUIS

ONE HUNDRED years ago the Vienna Medical School was honored by the presence of three men of worldwide reputation: Karl von Rokitansky, professor of pathology; Joseph Skoda, professor of internal medicine and Ferdinand von Hebra, professor of dermatology.

Ferdinand von Hebra was born on Sept. 7, 1816, and received his degree of Doctor of Medicine at the University of Vienna in 1841. Two of his teachers, Kolletschka, a friend of Semmelweis, and Karl von Rokitansky, both pathologists, had a great influence on Hebra's career. After graduation Hebra became an intern in internal medicine under the direction of the famous Skoda, at the Wiener allgemeines Krankenhaus. At that time there was no special department of dermatology in Vienna. Patients with skin diseases were isolated in a room called the "Scabiesstation." Skoda advised young Hebra to devote himself to the study of these diseases at this "Kraetzestation." The cruel treatment of these poor patients can be traced back to the Middle Ages, when all skin diseases were usually identified with leprosy or venereal diseases. In consequence, all dermatoses were considered to be contagious and the afflicted persons were regarded with contempt. Such was the situation when Hebra took over the clinic, where all patients, whether insane or affected with venereal diseases or scabies, were hospitalized together.

Medical science of this era was governed by the theory of morbid fluids, humoral medicine, as a cause of disease. There was no separation or differentiation of the various diseases according to etiology. Dermatology of a sort had been practiced before by men like Plenk, Willan, Alibert, Biett, and Rayner; however, their methods were individualistic and were soon forgotten after their deaths. Hebra based his research upon the teachings of Rokitansky and applied his knowledge of morphology to the interpretation of skin diseases. He expressed his basic conception later as follows: "The objective symptoms are the letters which are written onto the skin by the disease; it remains our task to decipher the writings." Skoda's modesty and farsightedness were demonstrated when he gave up his skin patients and proposed a separate clinic under the direction of Hebra.

Sarcoptes scabiei as the cause of scabies had been demonstrated many years before, but the general opinion prevailed that the disease was caused by morbid fluids. Hebra succeeded in proving the parasitic nature of scabies by repeated findings of the mite and by experimental inoculation. He described a number of new pictures of skin diseases, such as erythema exsudativum and prurigo, which

Read before the St. Louis-Kansas City Dermatological Society, St. Louis, March 26, 1950.

still bear his name; he described not only eczema more accurately than had been done before but also eczema marginatum, and on a trip to Scandinavia he coined the name "scabies norwegica." He advocated local therapy for skin diseases, a form of treatment which was regarded with disfavor by his colleagues for fear of "pushing the disease into the inner organs." Among the many medicants he introduced for local therapy, unguentum diachylon Hebrae was the most important. This ointment is still regarded highly in Europe, in contrast to the United States, where diachylon ointment is known only to older physicians. One of Hebra's therapeutic achievements which gave him international recognition was his waterbed. Today the waterbed is not only employed by dermatologists for severe burns, decubitus, pemphigus, and so on, but is also used in surgery, gynecology, internal medicine, and neurology.

Hebra was an excellent teacher. He received the title of an academic docent in 1844; he was appointed Primarius in 1848 and professor in December, 1849. Hebra, together with Elfinger and Heitzmann, published an atlas of dermatology and syphilology after twenty years of intensive work. Hebra's significance is based on his mastership in research and his personal talent as a teacher. He combined the art of the clinical diagnostician with the practical knowledge of an experienced therapeutist. As the founder of the famous Viennese school of dermatology one hundred years ago, he has well earned recognition throughout the world.

508 N. Grand Blvd.

THE TREATMENT OF GRANULOMA INGUINALE, LYMPHOGRANULOMA VENEREUM, CHANCROID, AND GONORRHEA

HARRY M. ROBINSON Jr., M.D.
BALTIMORE

PHYSICIANS interested in the treatment of venereal disease have been stimulated by the advent of the antibiotics to investigate the potentialities of these drugs in this field of endeavor. This discussion is concerned with the value of the commonly used antibiotics in the treatment of gonorrhea and its cutaneous manifestations, chancroid, lymphogranuloma venereum, and granuloma inguinale. More studies have been conducted to evaluate these drugs in the treatment of gonorrhea than in any other one of the venereal diseases, primarily because of the predominance of this infection. This report presents a review of the current literature as well as a summary of the work done in the department of dermatology and syphilology at the University of Maryland School of Medicine.

GONORRHEA

Penicillin.—There have been numerous reports attesting the value of penicillin in the treatment of gonorrhea.[1] It is an established fact that penicillin in doses sufficient to produce a clinical cure of this disease will also effectively mask the appearance of early syphilis for from one to four months or more. If this drug is used, the serologic status of the patient must be determined prior to its administration, and serologic tests for syphilis must be repeated at monthly intervals for four consecutive times. The work done at our clinic and reports from other sources indicate that the preparation of choice is penicillin procaine in aqueous solution or in oil, and that it should be administered in a single dose of from 75,000 to 300,000 units. The percentage of cures ranges from 92.7 to 100%, varying with the clinical reporting.

From the Department of Dermatology and Syphilology, University of Maryland School of Medicine.

Presented at a symposium on Venereal Diseases at the American Academy of Dermatology and Syphilology, Chicago, Dec. 6, 1950.

1. Alley, R. D.: Combined Penicillin and Chemotherapy in Acute Gonorrhea Urethritis, Yale J. Biol. & Med. **18**:7, 1945. Atcheson, D. W.: Penicillin Treatment for Gonorrhea, California & West. Med. **62**:164, 1945. Barringer, E. D.; Strauss, H., and Horowitz, E. A.: Penicillin Treatment in Sulfa-Resistant Cases of Gonorrhea in the Female, New York J. Med. **45**:52, 1945. Behr, S.: The Treatment of Sulfa-Resistant Gonococci with Penicillin, South African M. J. **18**:369, 1944. Bloomfield, A. L.; Rantz, L. A., and Kirby, W. M. M.: The Clinical Use of Penicillin, J. A. M. A. **124**:627 (March 4) 1944. Chinn, B. D., and Gillick, F. G.: Out-Patient Therapy of Gonorrhea, M. Ann. District of Columbia **14**:407, 1945. Christman, H. E.: Penicillin Therapy of Gonorrhea, Ohio M. J. **41**:426, 1945. Creswell, G. W., and Putnam, L. E.: Penicillin Therapy in Ambulatory Gonorrhea Patients, M. Ann. District of Columbia **14**:205, 1945.

Aureomycin.—Collins and his co-workers [2] reported on the effect of aureomycin in the treatment of 66 male patients and claimed good results in 49 with a dose of from 1 to 3 gm. They stated that their best results were obtained in those patients treated on two successive days and concluded that aureomycin was inferior to the effects of 300,000 units of penicillin in a "prolonging agent." In a later report [3] the conclusions as to the value of aureomycin in the treatment of gonorrhea had not changed.

Robinson [4] stated that 56 out of 70 patients with gonorrhea (80%) were cured with administration of 1 gm. of aureomycin. This is contrasted with a cure rate of 95% when an injection of 75,000 units of penicillin procaine in oil is given intramuscularly. In a series of patients treated at the University of Maryland clinic, 90% were cured with a single dose of 3 gm. of aureomycin. It is interesting to note at this time that 3 gm. of aureomycin in a single dose will also mask the appearance of syphilis, and the same precautions must be carried out with the administration of this drug as with penicillin.

Chloramphenicol.—In 1949 we [5] treated a series of 19 patients with chloramphenicol. We concluded that a single 3-gm. dose of this drug would cure gonorrhea, but it was not so effective when a larger amount was given in divided doses. Chen, Dienst, and Greenblatt [6] had only one failure in a group of 14 patients who were given 1 gm. of chloramphenicol three times a day for two days. This drug is also effective in masking syphilis when a 3-gm. dose is administered. This was effectively demonstrated in our own clinic.

Terramycin.—Hendricks and his co-workers [7] reported the cure of 15 patients with gonorrheal urethritis treated with terramycin. They used two doses of 1 gm. each given six hours apart. In our clinic, using a single dose of 3 gm., we have obtained cures on seven of the 11 patients (63.7%) treated. If this antibiotic is to be used in the treatment of gonorrhea, the same precautions must be observed as when penicillin is used, chloramphenicol, and aureomycin, because 3 gm. of terramycin will cause spirochetes to disappear from the moist lesions of early syphilis in from 24 to 48 hr. Serologic follow-up study must be instituted.

Streptomycin.—Putnam and his associates [8] gave four men with acute gonorrheal urethritis 0.1 gm. of streptomycin at hourly intervals for five doses. All four patients responded in 24 to 48 hr. by a reduction or cessation of the urethral dis-

2. Collins, H. S.; Paine, T. F., Jr., and Finland, M.: Clinical Studies with Aureomycin, Ann. New York Acad. Sc. **51**:231, 1948.

3. Collins, H. S.; Trousdale, H.; Kaiser, T. F.; Regan, F. C., and Finland, M.: Aureomycin Treatment of Acute Gonorrhea in Males, Am. J. Syph. **33**:263, 1949.

4. Robinson, R. C. V.: Aureomycin in the Treatment of Gonorrhea in the Male, Am. J. Syph. **34**:64, 1950.

5. Robinson, H. M., Sr., and Robinson, H. M., Jr.: Studies on Chloramphenicol in Early Syphilis and Gonorrhea, South. M. J. **42**:988, 1949.

6. Chen, C. H.; Dienst, R. B., and Greenblatt, R. B.: The Treatment of Gonorrhea with Chloramphenicol, South. M. J. **42**:986, 1949.

7. Hendricks, F. D.; Greaves, A. B.; Olansky, S.; Taggart, S. R.; Lewis, C. M.; Landman, G. S., and MacDonald, G. R.: Terramycin in the Treatment of Venereal Disease, J. A. M. A. **143**:4 (May 6) 1950.

8. Putnam, L. E.; Herweik, R. P.; Taggart, S. R., and Chinn, B. D.: The Treatment of Gonorrhea with Streptomycin, M. Ann. District of Columbia **16**:14, 1947.

charge. Taggart and his associates [9] were able to demonstrate 100% cures, using a dose of from 0.4 to 0.6 gm. The same workers stated that 0.5 gm. of streptomycin did not reduce the number of organisms visible on dark-field examination in 6, 12, and 24 hr., but they believe that a serologic follow-up study is just as important when this drug is used as when any other antibiotics are given.

Dihydrostreptomycin.—Taggart and his co-workers [10] concluded that dihydrostreptomycin is as effective as streptomycin in the management of gonorrhea. They treated 104 patients, using from 0.2 to 0.4 gm., and cured 95 of them. Jacoby and associates [11] reported a cure rate of 97.3% with a single injection of 1 gm. of the drug.

Treatment of Cutaneous Complications of Gonorrhea.—The effectiveness of any treatment of the cutaneous complications of gonorrhea must be gauged by its influence on (1) urethritis, (2) arthritis, (3) cutaneous eruption or keratosis, and (4) secondary infection of skin lesions.

TABLE 1.—*Gonorrhea*

Drug	Administration	Dose	Effectivity, %	Effect on Appearance of the Lesions of Early Syphilis
Penicillin	Injection (procaine penicillin in oil or aqueous solution)	75,000-300,000 units	95-99	Masks appearance
Penicillin	Oral (buffered tablets)	500,000 units; single dose	86-90	Masks appearance
Chloramphenicol	Oral	1-3 gm.; single dose	92.7-98	Masks appearance
Aureomycin	Oral	1-3 gm.; single dose	70-98	Masks appearance
Streptomycin	Injection	0.3-0.6 gm.	90	Does not mask in this dose
Dihydrostreptomycin	Injection	0.2-0.4 gm.	88-92	Does not mask in this dose
Terramycin	Oral	3 gm.; single dose	64	Masks appearance

Freireich, Schwartz, and Steinbrocker [12] stated that two of three patients with keratosis blennorrhagica obtained a good result when treated with penicillin. Thompson, White, and Hailey [13] reported the case of a man who had gonorrhea and keratosis blennorrhagica, who had a satisfactory response to treatment with penicillin. This same patient manifested gonorrhea some months later, and this attack was also followed by keratosis blennorrhagica, which this time failed to respond to therapy with penicillin when given to a total of 6,950,000 units. When this man was given streptomycin in doses of 0.4 gm. every four hours for 16 days,

9. Taggart, S. R.; Hirsh, H. L.; Hendricks, F. D.; Gable, G. R.; Puzak, M. A., and Greaves, A. B.: The Treatment of Gonorrhea with Streptomycin, Am. J. Syph. **33**:177, 1949.

10. Taggart, S. R.; Putnam, D. E.; Greaves, A. B., and Watson, J. A.: The Use of Dihydrostreptomycin in the Treatment of Gonorrhea, Am. J. Syph. **34**:62, 1950.

11. Jacoby, A.; Goldberg, W.; Sobel, N., and Rosenthal, T.: Treatment of Gonorrhea with Dihydrostreptomycin, Am. J. Syph. **34**:185, 1950.

12. Freireich, A. W.; Schwartz, S., and Steinbrocker, O.: Penicillin in the Treatment of Keratosis Blennorrhagica with Polyarthritis, Arch. Int. Med. **79**:239 (Feb.) 1947.

13. Thompson, R. G.; White, C. B., and Hailey, H.: Keratosis Blennorrhagica: Response to Streptomycin: Report of a Case, Arch. Dermat. & Syph. **59**:284 (March) 1949.

the lesions healed. Scott and Thomsen [14] reported the cases of two patients with primary cutaneous Neisseria gonorrhoeae infections which responded to penicillin therapy and of one patient who obtained a good result from sulfathiazole therapy. In two cases of keratosis blennorrhagica which have been under my observation the patients failed to respond to any of the currently used antibiotics. Smears and cultures of the urethral discharge had been positive for N. gonorrhoeae in both cases, but at the time of the dermatologic consultation there was complete absence of urethral discharge. Fortunately, this complication of gonorrheal urethritis is relatively rare, and so a long time will elapse before adequate work can be done to evaluate properly the effect of these antibiotics in the management of the cutaneous complications of this disease.

Summary of Treatment of Gonorrhea.—It is apparent from a survey of the literature and from personal experience that a single dose of from 75,000 to 300,000 units of penicillin procaine in oil suspension or aqueous solution given by injection is the most satisfactory treatment for gonorrheal urethritis. Precautions must be taken with follow-up serologic tests to avoid masking the appearance of early syphilis. Although no definite conclusions have been reached, it is quite possible that the antibiotics will prove to be of some value in the treatment of the cutaneous complications of gonorrhea.

CHANCROID

The methods in present-day use as diagnostic measures in chancroid are unsatisfactory and time-consuming. The presence of a positive reaction to the Ito-Reenstierna test does not indicate active infection. Although the inverse test, as done in our clinic, using diluted inactive bubo pus as an intradermal test in known reactors, is a conclusive diagnostic procedure, fluctuant buboes do not develop in all patients with chancroid, and therefore this method is of no value in those cases. Dienst and Gilkerson [15] believe that the diagnosis is made by exclusion. Positive cultures are difficult to obtain even from clinically characteristic lesions, and smears are of little value. Those who undertake to evaluate the effect of any drug in the treatment of chancroid have the added burden of first establishing the diagnosis.

Penicillin.—Strakosch, Kendell, Craig, and Schwemlein [16] reported on the penicillin treatment of 25 patients who had primary or secondary syphilis and coincidental chancroid. They stated that the small lesions healed in seven and one-half days. Five of their patients needed additional sulfathiazole. Lahiri [17] was enthusiastic about the effect of penicillin upon the 10 patients he treated. Routine smears, cultures, and intradermal tests are not made for chancroid in every patient with genital lesions of early syphilis, and therefore it is quite possible that many of these patients have a coincidental infection with Hemophilus ducreyi and are benefited by the penicillin therapy.

14. Scott, M. J., and Thomsen, J.: Primary Cutaneous Neisseria Gonorrhoeae Infections, Am. J. Syph. **34**:262, 1950.

15. Dienst, R. B., and Gilkerson, S. W.: Evaluation of the Ducrey Skin Test for Chancroid, Am. J. Syph. **31**:65, 1947.

16. Strakosch, E. A.; Kendell, H. W.; Craig, R. M., and Schwemlein, G.: Clinical and Laboratory Investigation of 370 Cases of Chancroid, Invest. Derm. **6**:95, 1945.

17. Lahiri, K. D.: Penicillin in Chancroid, J. Indian M. A. **15**:406, 1946.

Aureomycin.—Zheutlin and Robinson [18] treated three patients whose infections were diagnosed as chancroid with aureomycin, using 0.5 gm. four times daily for seven to 14 days. Healing was complete in all three patients at the termination of therapy. Long and his associates [19] listed penicillin and aureomycin as being of equal value in the treatment of chancroid.

Terramycin.—Experimental studies [20] indicate that terramycin is of value against H. influenzae and Hemophilus pertussis. In view of this fact it is quite possible that terramycin may also be of value in treatment of infections with H. ducreyi, but as yet no clinical reports are available.

Chloramphenicol.—R. V. Robinson and Zheutlin [21] reported a successful result in a Negro woman who had lesions on the labia. They gave her 0.5 gm. of chloramphenicol four times daily for 13 days. This is the only report in the literature referring to the effect of this drug on chancroid.

Streptomycin and Dihydrostreptomycin.—Mortara and Saito [22] reported that all the strains of H. ducreyi that they tested were sensitive to streptomycin. These same men used this drug successfully as a prophylactic and treatment agent in

TABLE 2.—*Chancroid*

Drug	Administration	Dose	Effectivity	Effect on Appearance of the Lesions of Early Syphilis
Penicillin	Injection	300,000-600,000 units daily	Value questionable	Masks
Chloramphenicol	Oral	0.5 gm. four times daily for 13 days	Healing of lesions reported	Masks
Aureomycin	Oral	0.5 gm. four times daily for 7 to 14 days	Healing of lesions reported	Masks
Terramycin	Insufficient data	.....	.....	.....
Streptomycin	Injection	0.5-1 gm. four times daily	Healing of lesions reported	No effect
Dihydrostreptomycin	Injection	0.5-1 gm. four times daily	Healing of lesions reported	No effect

experimentally produced chancroid.[23] Taggart and his co-workers [24] treated 61 patients with this disease with streptomycin. They established the diagnosis on the basis of a positive culture from the lesions or from pus of a bubo, a positive smear, or a positive reaction to Ducrey test. Buboes were present in 19 patients, and six had previously received sulfonamides with little or no improvement. Some of these patients received 1 gm. four times daily until the lesions healed and some 1 gm. daily for five days. The authors stated that streptomycin was a valuable drug in

18. Zheutlin, H. E. C., and Robinson, R. C. V.: Aureomycin in the Treatment of Chancroid: A Report of 3 Cases, Am. J. Syph. **34**:71, 1950.

19. Long P. H.; Chandler, C. A.; Bliss, E. A.; Bryer, M. S., and Schoenbach, E. B.: The Use of the Antibiotics, J. A. M. A. **141**:315 (Oct. 1) 1949.

20. Brochure, Charles Pfizer & Company, Inc., Brooklyn.

21. Robinson, R. C. V., and Zheutlin, H. E. C.: Unpublished data, cited by Robinson, R. C. V.: Am. J. Syph. **34**:273, 1950.

22. Mortara, F., and Saito, M. T.: Sensitivity of Hemophilus Ducreyi to Antibiotic and Other Substances in Vitro, Am. J. Syph. **30**:352, 1946.

23. Mortara, F., and Saito, M. T.: Streptomycin in Experimental Chancroid, Am. J. Syph. **31**:20, 1947.

24. Taggart, S. R.; Hirsh, H. L.; Hendricks, F. D.; Gable, G. R.; Puzak, M. A., and Greaves, A. B.: The Treatment of Chancroid with Streptomycin, Am. J. Syph. **33**:180, 1949.

the treatment of chancroid but that its use was impractical because of the necessity for hospitalization and the cost to the patient. It was their belief that it was indicated for those patients who did not respond to sulfonamides. Weber and his associates [25] reported the case of a patient with sulfonamide-resistant chancroid whom they treated with streptomycin without a beneficial result.

Summary of Treatment of Chancroid.—Before therapy with any one of the antibiotics is instituted for chancroid, the presence or absence of early syphilis must be carefully determined, because all these drugs, with the possible exception of streptomycin and dihydrostreptomycin, will mask its appearance and may prevent the development of a positive serologic reaction for syphilis for from one to four months or more. Careful dark-field examinations must be performed. The antibiotics should be used in the treatment of chancroid only when the sulfonamides have failed to produce a satisfactory result.

LYMPHOGRANULOMA VENEREUM

It is difficult to evaluate the effect of any drug in the treatment of lymphogranuloma venereum unless a bubo is present. The more chronic lesions, such as rectal stricture or chronic sinuses, would not be expected to respond to chemotherapy with complete healing without the benefit of surgical intervention. It is unfortunate that there is not some simple reliable procedure of value in the diagnosis of this condition. A positive reaction to a Frei test does not indicate the presence of active disease. The inverse Frei test is a satisfactory and dependable means of diagnosis but can be performed only in an acute case in which there is a bubo present, and the complement-fixation test is of doubtful value. As in the case of chancroid, the physician who undertakes the evaluation of a drug in this condition must first establish the diagnosis.

Penicillin.—On the basis of experimental infection with the virus of lymphogranuloma venereum, Heilman [26] concluded that if it were used in relatively large doses penicillin might exert a protective effect but that it would be of limited value in the treatment of the infection in man. It has been our experience at the University of Maryland Clinic that penicillin is not indicated in the treatment of lymphogranuloma venereum.

Aureomycin.—Long and his co-workers [19] list aureomycin as the drug of choice in the treatment of lymphogranuloma venereum. From their experience in the management of 49 patients, Wright and his associates [27] concluded that this drug

25. Weber, W. D.; Williams, J. H., and Huffines, T. R.: Streptomycin Therapy in a Case of Sulfonamide-Resistant Hemophilus Ducreyi (Chancroid) Infection, Am. J. Syph. **33**:58, 1949.

26. Heilman, F. R.: Effect of Penicillin on Experimental Infections with the Virus of Venereal Lymphogranuloma, Proc. Staff Meet., Mayo Clin. **21**:237, 1946.

27. (*a*) Wright, L. T.; Sanders, M.; Logan, M. A.; Prigot, A., and Hill, L. M.: The Treatment of Lymphogranuloma Venereum and Granuloma Inguinale in Humans with Aureomycin in Symposium on Aureomycin, a New Antibiotic, New York, July 21, 1949. (*b*) Wright, L. T.; Sanders, M.; Logan, M. A.; Prigot, A., and Hill, L. M.: The Treatment of Lymphogranuloma Venereum and Granuloma Inguinale in Humans with Aureomycin, Ann. New York Acad. Sc. **51**:318, 1948. (*c*) Wright, L. T.; Sanders, M.; Logan, M. A.; Prigot, A., and Hill, L. M.: Aureomycin: A New Antibiotic with Virucidal Properties, J. A. M. A. **138**:408 (Oct. 9) 1948. (*d*) Prigot, A.; Wright, L. T.; Logan, M. A., and deLuca, F. R.: Anorectogenital Lymphogranuloma Venereum and Granuloma Inguinale Treated with Aureomycin, New York J. Med. **49**:1911, 1949.

was the one to be preferred. Eight of their patients had buboes which reduced in size after four days of administration of the antibiotic. One patient who had rectal bleeding experienced relief of symptoms after three days of treatment. R. C. V. Robinson, Zheutlin, and Trice [28] treated nine patients for whom they had established the diagnosis by a positive Frei test and a positive complement-fixation test for lymphogranuloma venereum. They were not impressed with the value of the drug in the therapy of this disease. Benhamou and his co-workers [29] reported on the spectacular cure of this condition with oral administration of aureomycin. Prigot and associates [27d] were enthusiastic about the results they obtained in treating 14 Negro patients with buboes. They stated that there was no beneficial effect on strictures but that pain was diminished and rectal discharge stopped.

Chloramphenicol.—From their results in the treatment of three patients with chloramphenicol, R. C. V. Robinson and his associates [30] felt that this drug was of little value in the management of lymphogranuloma venereum. Smadel and his co-workers [31] reported that 3 gm. of this drug every eight hours for 14 days had

TABLE 3.—*Lymphogranuloma Venereum*

Drug	Administration	Dose	Effectivity	Effect on Appearance of the Lesions of Early Syphilis
Penicillin	Injection	300,000-600,000 units daily	No value	Masks
Chloramphenicol	Oral	6 gm. daily	Fair response	Masks
Aureomycin	Oral	3-4 gm. daily for 6-15 days	Fair response	Masks
Terramycin	Oral	1 gm. daily 4 times for 14 days	One good result reported	Masks
Streptomycin	Insufficient data	.....	.....	.....
Dihydrostreptomycin	Insufficient data	.....	.....	.....

induced clinical cure, although the elementary body might still be found in the tissues. Woodward [32] treated three patients with 30 to 36 gm. over a 14-day period with good results.

Terramycin.—The Pfizer brochure reports a successful result in the treatment of lymphogranuloma venereum with 1 gm. of terramycin every six hours for 13 days.

Streptomycin and Dihydrostreptomycin.—There are insufficient data to warrant any statement as to the value of streptomycin and dihydrostreptomycin in the treatment of this disease.

28. Robinson, R. C. V.; Zheutlin, H. E. C., and Trice, R.: Treatment of Lymphogranuloma Venereum with Aureomycin, Am. J. Syph. **34**:67, 1950.

29. Benhamou, E.; Destaing, F.; Gauthier, J., and Sorrel, G.: Maladie de Nicolas-Favre à forme bubonique guérie spectaculairement par l'auréomycine donnée par voie orale, Bull. et mém. Soc. méd. hôp. Paris **65**:832, 1949.

30. Robinson, R. C. V.: Newer Antibiotics in Treatment of Venereal Disease, Am. J. Syph. **34**:273, 1950.

31. Smadel, J. E., and Jackson, E. B.: Effect of Chloromycetin on Experimental Infection with Psittacosis and Lymphogranuloma Venereum Viruses, Proc. Soc. Exper. Biol. & Med. **67**:478, 1948.

32. Woodward, T. E.: Unpublished data.

Summary of Treatment of Lymphogranuloma Venereum.—The antibiotics of choice in the treatment of lymphogranuloma venereum are aureomycin or chloramphenicol.

GRANULOMA INGUINALE

Demonstration of the bacillary nature of Donovan body by Anderson and her associates [33] led Barton, Craig, Schwemlein, and Bauer [34] to try streptomycin as a therapeutic measure against granuloma inguinale. Thus a great advance was made in the treatment of this devastating disease. With the development of other antibiotics more studies have been conducted to determine their value in the therapy of this condition.

Penicillin.—Nelson [35] and Haserick [36] demonstrated that penicillin was of no value in the treatment of granuloma inguinale. This has been our experience also.

Streptomycin.—As previously stated, the work done by Barton and his associates [34] demonstrated that streptomycin caused the lesions of granuloma inguinale to heal completely. They stated that Donovan bodies disappeared from the lesions in from 10 to 20 days. Kupperman, Greenblatt, and Dienst [37] treated 48 patients with streptomycin, and in some of their patients they noted disappearance of Donovan bodies from the lesions in four to five days and absence of these bodies from the lesions of all their patients in 14 days. Another fact established by this early trial was the almost immediate relief from pain experienced by all patients. The dose ranged from 3.3 gm. in five days to 60 gm. in 62 days. These authors recommended a five-day course of treatment in which a total dose of 20 gm. of the drug is given. In 91 cases they noted eight recurrences when 2 gm. or less a day was given. In our clinic we have administered 4 gm. a day for 10 days with excellent results. Stewart and Laur [38] had satisfactory results with the administration of 20 gm. in a 5-to-15-day period. Jacoby and his co-workers [39] treated 37 patients in the outpatient department with a single daily dose of 3 gm. in aqueous solution, or in oil and wax, and concluded that this was a satisfactory method of therapy.

Dihydrostreptomycin.—In the same dosage as that of streptomycin, dihydrostreptomycin has proved to be as effective as streptomycin with fewer side reactions.

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33. Anderson, K.; DeMonbreun, W. A., and Goodpasture, E. W.: An Etiologic Consideration of Donovania Granulomatis Cultivated from Granuloma Inguinale (3 Cases) in Embryonic Yolk, J. Exper. Med. **81**:25, 1945.

34. Barton, R. L.; Craig, R. M.; Schwemlein, G., and Bauer, T. J.: Granuloma Inguinale Treated with Streptomycin, Arch. Dermat. & Syph. **56**:1 (July) 1947.

35. Nelson, R. A.: Penicillin in Treatment of Granuloma Inguinale, Am. J. Syph. **28**:611, 1944.

36. Haserick, J. R.: The Failure of Penicillin in the Treatment of Granuloma Inguinale, Arch. Dermat. & Syph. **52**:182 (Sept.) 1945.

37. Kupperman, H. S.; Greenblatt, R. B., and Dienst, R. B.: Streptomycin in the Therapy of Granuloma Inguinale, J. A. M. A. **136**:84 (Jan. 10) 1948.

38. Stewart, J. J., and Laur, W. E.: Streptomycin Therapy of Granuloma Inguinale, Am. J. Syph. **33**:65, 1949.

39. Jacoby, A.; Rosenthal, T., and Sobel, N.: Ambulatory Treatment of Granuloma Inguinale with Streptomycin, Am. J. Syph. **33**:76, 1949.

Chloramphenicol.—Greenblatt and associates [40] reported excellent results in the treatment of five patients when they used 20 gm. of chloramphenicol in from five to 10 days. Robinson and Cronk [41] treated 13 patients with doses of 20 to 40 gm. divided into 500 mg. four times daily for 10 days. Patients treated with larger doses did not suffer relapses. It is interesting to note that three of their patients failed to respond to treatment with aureomycin but did have a good result from treatment with chloramphenicol.

Aureomycin.—Wright and his co-workers [27b] were the first to observe the beneficial effect of aureomycin in the treatment of granuloma inguinale. Subsequent to this, Greenblatt and his associates [42] reported the drug to be effective in the management of streptomycin-resistant infections. R. C. V. Robinson, Elmendorf, and Zheutlin [43] found that intramuscular injection of aureomycin was not only painful but also less effective than streptomycin. When they administered the drug by mouth in doses of 40 gm., they obtained an initial satisfactory result in 27 out of 36 cases. In a later publication they concluded that aureomycin, when

TABLE 4.—*Granuloma Inguinale*

Drug	Administration	Dose	Effectivity	Effect of Appearance of the Lesions of Early Syphilis
Penicillin	Injection	300,000-600,000 units daily	No value	Masks
Chloramphenicol	Oral	20-40 gm. (divided doses) in 10 days	Donovan bodies disappear in 5-7 days; lesions heal promptly	Masks
Aureomycin	Oral	3-5 gm. daily for 15 days	Lesions heal promptly	Masks
	Injection	200-500 mg. daily for 15 days	Lesions heal promptly	Masks
Terramycin	Oral	3 gm. daily for 15 days	Lesions heal promptly; Donovan bodies disappear in 3 to 7 days	Masks
Streptomycin	Injection	20-30 gm. in 5 to 10 days	Donovan bodies disappear in 5 to 9 days; lesions heal promptly	No effect
Dihydrostreptomycin	Injection	20-30 gm. in 5 to 10 days	Donovan bodies disappear in 5 to 9 days; lesions heal promptly	No effect

administered orally, was more effective than streptomycin in at least five cases. They believe that 20 gm. in 10 days is the minimum effective dose. In the clinic at the University of Maryland three patients with granuloma inguinale were treated by us with intravenous injections of aureomycin hydrochloride, 200 mg. being given daily for 15 days to two patients and 300 mg. daily for 15 days to the other. Relief from pain was prompt, and healing of lesions was complete. It is interesting to note that the healing process continued in one case after the daily injections were discontinued.

Terramycin.—Hendricks and his co-workers [7] reported disappearance of Donovan bodies from the lesions of two patients on the third day of administration of

40. Greenblatt, R. B.; Wammock, V. S.; Dienst, R. B., and West, R. M.: Chloromycetin in the Therapy of Granuloma Inguinale, J. M. A. Georgia **38**:206, 1949.

41. Robinson, R. C. V., and Cronk, B.: Unpublished data.

42. Greenblatt, R. B.; Dienst, R. B.; Chen, C. H., and West, R.: Oral Aureomycin in the Therapy of Streptomycin-Resistant Granuloma Inguinale, South. M. J. **41**:1121, 1948.

43. Robinson, R. C. V.; Elmendorf, D. F., Jr., and Zheutlin, H. E. C.: Aureomycin in the Treatment of Granuloma Inguinale, Am. J. Syph. **33**:389, 1949.

terramycin. They used a dose of 60 mg. per kilogram of body weight per day for 12 days. They noticed excellent clinical healing in both cases. Thus far we have used terramycin in the treatment of one patient with severe granuloma inguinale of long duration. We used an initial dose of 3 gm., followed by 0.5 gm. every three hours to a total of 48 gm. In order to insure proper administration of the drug, the patient was hospitalized. Donovan bodies were still present six days after institution of treatment, but four days later the lesions had become completely epithelialized, and up to this time there has been no relapse.

Summary of Treatment of Granuloma Inguinale.—The value of streptomycin, dihydrostreptomycin, aureomycin, and chloramphenicol in the treatment of granuloma inguinale has been definitely proved. There is no longer any doubt that the administration of any one of these drugs produces a result that is far superior to that obtained by any method of therapy which has been used previously. Preliminary studies indicate that terramycin may also be of value in the treatment of this disease, but further investigation will be necessary to prove this.

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CLINICAL STUDIES IN PERCUTANEOUS ABSORPTION

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THERE is a trend on the part of dermatologists toward prescription of washable ointment bases as vehicles for medicinals employed in topical therapy. The recognition of the fact that there is considerably increased absorption of therapeutic agents from such bases in comparison with the absorption from the traditional oleaginous bases has led to the present investigation, which is concerned with the quantitative evaluation of the comparative increase in absorption.

An increase in the absorption and penetration of medicinals from ointment bases has obvious advantages. The release of antiseptics incorporated into water-soluble bases has been shown to be more rapid and complete than that from water-immiscible bases[1]; diffusion of medicaments into the diseased area occurs more readily, and lower concentrations of active ingredients suffice to produce a comparable therapeutic response, this fact resulting in considerable saving in cost with expensive medicinals. On the other hand, indiscriminate use of such vehicles containing high concentrations of active medicinal agents over extensive areas of diseased skin may lead to absorption of the drugs to such a degree that toxic manifestations may result. Fatalities due to excessive absorption have been reported in cases of external application of sulfur and of salicylic acid.[2]

One of us has observed mild mercurial stomatitis in a patient being treated for generalized psoriasis. The treatment consisted in application to the body of 5% ammoniated mercury and 2.5% salicylic acid in an oleaginous vehicle and to the scalp of the same agents in a like concentration in a washable base, plus fever therapy, which possibly enhanced absorption, every other day. The symptoms of stomatitis subsided soon after discontinuance of treatment with the mercurial preparation.

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1. Meyers, D. B.; Nadkarni, M. V., and Zopf, L. C.: J. Am. Pharm. A. (Scient. Ed.) **38**:231, 1949.

2. Strakosch, E. A.: Studies on Ointments: Ointments Containing Sulphur, Arch. Dermat. & Syph. **47**:216 (Feb.) 1943. Sannicaudro, G.: Dermasifilografia **12**:273, 1937.

Several methods of determining absorption of therapeutic agents from topical vehicles have been described in the literature, and numerous modifications of these methods have been suggested. Neuroth and Lee [3] have summarized the procedures employed by various investigators, which include both in vitro [4] and in vivo [5] methods of determination. Although some correlation is evident in the results of these workers, much of the literature concerning absorption is contradictory, mainly because of variations in procedures and controls. The precise evaluation of penetration and absorption of medicaments from topical vehicles depends upon the control of several factors which may produce inconsistencies in the results. These factors include the therapeutic agent employed, its relative solubility in the vehicle, the environmental temperature, the condition of the skin area tested, the size and site of application, and the sex and age of the person tested. It is also necessary to eliminate the possibility of contamination of larger areas of skin outside the test site, to prevent introduction of the agent by routes other than the skin, to avoid the subject's coming into contact with other chemicals which might distort the results of the test, and to insure that the procedures be carried out methodically and exactly for all the persons tested.

Earlier work from this laboratory [1] was concerned with the study of absorption and penetration of potassium iodide and phenolsulfonphthalein from washable polyethylene glycol (carbowax®) vehicles through the intact skin of albino rats. A change in the rate and amount of absorption caused by the addition of small percentages of silicon dioxide, cetyl alcohol, wool fat, petrolatum, or a tergitol® (surface-active agent) was demonstrated. With the use of a modified agar-cup method, a study was also made of the release of antiseptics from the same vehicles. Our current study is a continuation of this original work on absorption, as applied to the human skin.

The experimental work was designed with the idea of making a quantitative evaluation of the absorption of medicaments through the human skin from a water-soluble base in comparison with that obtained from a petrolatum base. Phenolsulfonphthalein was employed as the tracer agent.

The water-soluble base (Base 1) was a mixture of equal parts of polyethylene glycol 4000 and polyethylene glycol 400. It was prepared by warming the two components together on a water bath to 70 C. and allowing the mixture to cool, with constant stirring until congealed. This formula is representative of a completely water-soluble anhydrous base. Its choice was further indicated by the fact that it is official in the fourteenth revision of the United States Pharmacopoeia, as polyethylene glycol ointment. White petrolatum U. S. P. was used for comparative study. The selection of this oleaginous vehicle, in preference to white ointment or other similarly formulated bases, was made with the idea of eliminating modifying

3. Neuroth, M. L., and Lee, C. O.: J. Am. Pharm. A. (Pract. Pharm. Ed.) **6**:285, 1945.

4. Luff, A. P.: Pharm. J. **50**:206, 1891. Breslauer, E.: Ztschr. f. Hyg. u. Infectionskr. **20**:165, 1895. Craw, R. O., and Lee, C. O.: Pharm. Arch. **9**:1, 1938. Seelman, J. V.: Absorption of Drugs and Poisons Through the Skin, Correspondence, J. A. M. A. **110**:1127 (April 2) 1938.

5. Brown, E. W., and Scott, W. O.: J. Pharmacol. & Exper. Therap. **50**:273, 1934. Macht, D. I.: Absorption of Drugs and Poisons Through Skin and Mucous Membranes, J. A. M. A. **110**:409 (Feb. 5) 1938. Duemling, W. W.: Wetting Agents: New Synthetic Chemicals of Use in Finer and More Efficient Topical Dermatologic Therapy, Arch. Dermat. & Syph. **43**:264 (Feb.) 1941.

factors such as hydrous wool fat and the higher alcohols, which have been demonstrated to affect the rate and amount of absorption of medicinal agents from the base.

Phenolsulfonphthalein was selected as the tracer material because of the accuracy with which amounts of it can be quantitatively determined in the urine by standard photoelectric procedures. The almost complete elimination of this dye by the kidneys made it possible for us to obtain a reasonably accurate picture of the absorption. Further, the insoluble nature of this dye in both types of bases removed to a great extent the factor of differential absorption and penetration due to variance in solubility in the topical media. Its nontoxicity and noninterference with other medication employed during hospitalization were added factors which favored its selection.

The ointments were prepared by incorporating the required amount of the finely powdered phenolsulfonphthalein into the base.

The subjects of the experiments were hospitalized patients of the dermatology and syphilology wards in the University of Iowa Hospitals. They were selected at random irrespective of sex, age, or race. Patients under treatment with methylrosaniline chloride topically were excluded from this study because this dye was absorbed and excreted in sufficient quantity to interfere with the analysis of urine for phenolsulfonphthalein. Where the test would cause undue discomfort the patient was excused from the experiment. None of the patients tested had known renal disease; it was felt that the amount of dye applied was sufficiently large, the amount excreted so relatively small, and the time of collection so prolonged that minor renal abnormalities would not manifest themselves in the results.

It was necessary to carry out certain preliminary trials in order to determine the best method of application of the ointment, size and site of application, concentration of the dye in the ointment, and length of time of application. Comfort of the patient and protection of the ointment during the period of application were the main considerations in the choice of the location and size of the area tested. In the first experiments 10 gm. of the ointment, containing 3.85% of phenolsulfonphthalein, was applied to an area measuring 5 by 10 in. (12.5 by 25.0 cm.) on the lateral aspect of the chest and covered with a layer of plastic cloth for protection. However, difficulty was experienced in keeping the covering material in place, with resultant loss of the ointment from the skin and spread of the ointment beyond the test site. It was also impossible to eliminate or control the degree of friction produced by the normal activity of the patient. In further experiments, the concentration of the dye was increased, the amount of ointment and the size of the area of application were reduced, and the method of protection of the test area was changed.

The most suitable method found, and the one employed in obtaining the results of our study, was as follows:

Five grams of the ointment, containing 7.7% of phenolsulfonphthalein, was spread uniformly, without undue inunction, on the lateral aspect of the chest of the patient by means of a wooden tongue depressor over a circular area 4½ in. (11 cm.) in diameter (16 sq. in. [40 sq. cm.]). The application was then covered with a pliable plastic shield, which was also circular, 5 in. (12.5 cm.) in diameter and 2 in. (5.0 cm.) deep. This shield was secured with adhesive tape except where there was existing dermatitis or known sensitivity to the tape; in such cases the shield was covered with a square of surgical gauze and held in place with elastic bandages wrapped around the chest. The application was made in the morning; 12 hr. later the ointment was removed as completely as possible, with minimum friction, with a dry gauze sponge, the possible modifying influence of detergents, organic solvents, or water, thus being avoided.

Collection of the urine began as soon as the ointment was applied, and separate specimens for the first and second 24-hr. periods were obtained. It had been previously determined that urine collected after the first 48 hr. contained negligible amounts of phenolsulfonphthalein and that after one week the patient could be reemployed as a subject for further tests. Without resort to catheterization, it was impossible to delimit exactly the two collection periods, and some minor variation might occur, particularly with regard to the comparative excretions on the first and second days. The possibility of incomplete collections could not be eliminated in the case of unintelligent, forgetful, or uncooperative patients, but these apparently occurred quite infrequently.

The estimation of phenolsulfonphthalein excreted in the urine was made by means of a photoelectric colorimeter previously standardized against samples containing known amounts of the dye. The instrument was compensated to filter out any color other than the pink or red of the test material by the use of a suitable filter which eliminated light of wave lengths below 5,300 A. The volume of each urine sample was measured, and those under 1,000 cc. were diluted to 1 l., as the standardization of the instrument was made on the basis of milligrams of phenolsulfonphthalein per liter. One cubic centimeter of a 10% solution of sodium hydroxide was added to insure a definitely alkaline pH, and the mixture was centrifuged at 3,000 rpm for 10 min. to free it from turbidity. The clear supernatant fluid was then placed in the photoelectric cell of the colorimeter and the number of milligrams of phenolsulfonphthalein per liter computed from the reading observed.

TABLE 1.—*Average Excretion Levels, in Milligrams, of Phenolsulfonphthalein*

	White Petrolatum *		Carbowax® Base 1 *	
	24 Hr.	48 Hr.	24 Hr.	48 Hr.
Normal Skin				
All patients	0.87 (70)	1.56 (64)	1.05 (64)	1.77 (58)
0-34 yr.	0.68 (17)	1.19 (15)	1.04 (13)	1.58 (12)
35-64 yr.	1.04 (38)	1.86 (34)	1.09 (37)	1.90 (32)
65 yr. and over	0.66 (15)	1.23 (15)	0.90 (14)	1.65 (14)
Men	1.03 (16)	1.89 (13)	1.12 (31)	1.94 (27)
Women	0.82 (54)	1.47 (51)	0.99 (33)	1.63 (31)
Dermatitis	1.63 (13)	2.45 (11)	3.49 (20)	4.85 (20)

* Figures in parentheses indicate the number of tests included.

RESULTS

In spite of the variable factors noted earlier in this report, the results were remarkably uniform, both in repeated tests on the same person and comparatively in different patients. The effects of uncontrolled variables were manifested by occasional very high or very low figures; in several cases where high results occurred unexpectedly, contamination of mucous surfaces or of the container of urine was noted; in other cases surreptitious self-medication with phenolphthalein in proprietary laxatives was suspected; occasional extremely low figures were usually accompanied with a very low volume of urine, suggesting incomplete collection. Where such wide variations were subject to likely or provable explanation, the figures were not included in computing the averages; the discharge of patients before completion of the test invalidated other data; in all, 134 patient-trials out of a total of 190 were utilized. The results of these 134 trials were averaged into several groups, as follows: the average excretion of phenolsulfonphthalein for the 24- and 48-hr. periods in the group tested on normal skin with white petrolatum; the average excretion for the same periods in the group tested on the normal skin with Base 1; the average excretion in both groups further classified by age and by sex; and, finally, the average excretion in patients tested on areas of diseased skin with both bases. These averages appear in Table 1.

In addition to the 190 trials carried out on 59 patients in the actual experiment, another 52 trials on 35 patients were run during the preliminary period; of these 242 applications to 94 patients, ranging from one to 12 tests on each person, none produced any evidence of sensitization to either vehicle. One person, hospitalized because of a widespread therapeutic contact dermatitis, showed an erythematous reaction to the application on two consecutive weeks, after five consecutive weekly tests without incident; patch tests gave positive reactions to 7.7% phenolsulfonphthalein in both bases but negative ones to the vehicles alone.

COMMENT

Because of the variable factors which have already been discussed, the quantitative results cannot be accorded strict significance, but the over-all uniformity of the results permits certain valid generalizations concerning the ability of the normal and abnormal human skin to absorb a water- and oil-insoluble substance from a water-soluble and an oleaginous vehicle. These studies are continuing and will be concerned with the ability of the skin to absorb water-soluble substances from these vehicles, as well as with possible differences introduced by the testing of manifestly hairy areas of the body; the results will form the basis of future reports. It is possible that the results noted with phenolsulfonphthalein will not be quantitatively the same as those observed with other insoluble medicaments, but it seems likely that the absorption will be in generally similar quantity, varying perhaps with comparative insolubility and molecular size.

Normal Skin.—On a basis of these studies it appears that the normal and relatively hairless human skin absorbs the insoluble tracer dye phenolsulfonphthalein in small but fairly constant amounts from both a polyethylene glycol vehicle (Base 1) and petrolatum. With the former the excretion is about 20% greater than with the latter during the first 24 hr., and 15% greater for the entire 48-hr. period.

Age.—The patients were grouped arbitrarily by age in order to determine whether there was a significant difference in the absorption rates for young, middle-aged, and old persons, and particularly whether senility of the skin influenced absorption. Senility in its incipient stages is so difficult to delineate that the separation into age groups was felt to be the only satisfactory way to determine the effect of this factor. The limiting ages were chosen as 0 to 34, 35 to 64, and 65 and older. The actual ages were 10 to 34, 35 to 64, and 65 to 78. It was expected that the older patients would not absorb the dye as well as the general average, and this proved to be true, the excretion over the 24- and 48-hr. periods being 9 to 37% less for these persons than for the middle-age group; there was less difference in the groups tested with the polyethylene glycol vehicle than in those tested with petrolatum. We expected no significant difference between the younger and the middle-age groups, but absorption was found to be definitely lower in the younger patients, their excretion levels averaging almost exactly the same as those in the oldest group. The diminished absorption in the young and old was not due to preponderant differences in age, sex, or race, the distribution of those factors being quite even throughout.

Sex.—Results of tests conducted on normal skin sites were further grouped according to the sex of the patient. Although no difference was expected, the results showed that the male skin absorbed the dye in definitely larger quantities than did that of the women. The excretion in the first 24 hr. was 13% higher in men than in women tested with the polyethylene glycol vehicle (Base 1) and 26% higher

in men than in women tested with petrolatum. For the total 48-hr. period the excretion averaged 19% higher in men than in women tested with the water-soluble vehicle, and 29% higher in men than in women tested with the oleaginous base.

We cannot explain these differences in results corresponding to sex and age, but whether differences in oiliness, sweatiness, coarseness, hairiness, or other characteristics, or combinations thereof, produce these variations will be the subject of further investigations.

Race.—There was no apparent difference between the absorption by the deeply pigmented skin of the Negro and American Indian and that by the skin of white persons, but the number of patients of the former two races was too small to permit any definite opinion to be formed.

Dermatitis.—The excretion levels for patients on whom the ointment was applied to areas of dermatitis were tabulated separately. All patients whose test sites were either erythematous or eczematous were grouped together according to the vehicle applied. It was impossible to grade the dermatitis in any way, but it was clearly

TABLE 2.—*Amounts of Phenolsulfonphthalein Excreted by R. W. During Weekly Tests on Diseased Skin*

Date	Condition of Skin	Phenolsulfonphthalein Excreted, Mg.	
		24 Hr.	48 Hr.
2/15/49	Very red and oozing	10.20	11.00
2/22/49	Improved; mild oozing	4.75	5.85
3/ 1/49	Improved; slight oozing	4.00	5.50
3/ 8/49	Severe exacerbation with marked oozing	7.50	10.48
3/15/49	(Patient excused because of discomfort)	.....	.....
3/22/49	.....	.....	.....
3/29/49	Red, scaling dermatitis with slight oozing	3.01	4.53
4/ 5/49	Dry and scaling, with subsiding erythema	3.08	3.98

apparent that the absorption from either vehicle was far higher through an oozing surface than through an unbroken erythematous surface but definitely greater through either than through the normal intact skin. The amount of phenolsulfonphthalein excreted by all patients tested in areas of dermatitis with the white petrolatum vehicle averaged twice that for persons with normal skin using the same base; individual patients excreted from 115 to 340% of the normal during the first 24 hr. Absorption of the dye through areas of dermatitis from the polyethylene glycol vehicle (Base 1) yielded excretion levels averaging three and one-half times the normal for that base, with individual patients excreting from 130 to 970% of the normal. Furthermore, the excretion of the dye averaged twice as high in patients tested in areas of dermatitis with the polyethylene glycol vehicle (Base 1) as those tested with petrolatum; individual values ran four and five times higher with the water-soluble base. The same general findings hold for the total 48-hr. excretion of the dye.

It was also noted that when testing was repeated on a diseased skin over a period of several successive weeks the excretion of phenolsulfonphthalein paralleled the improvement and relapses in the dermatitis. Table 2 illustrates this phenomenon in a patient, R. W., 58, with a generalized oozing dermatitis, seborrheic in nature and complicated by therapeutic contact dermatitis.

Two other types of skin lesions, namely hyperkeratotic dermatoses and ulcers of the skin, might be expected to yield different results on the absorption tests but were not available for study during the course of this preliminary work.

CONCLUSIONS

1. On the normal human skin the use of a water-soluble vehicle promotes greater absorption of an insoluble dye (phenolsulfonphthalein) incorporated therein than does the use of an oleaginous base. The skin of persons in the age range of from 35 to 64 absorbed the dye more rapidly and in greater quantity than did the skin of those either younger or older. This statement held true for either base, but the differences were greater with the oleaginous vehicle. With either base the average male skin has greater absorptive ability for the dye than does the average woman's skin. These differences are relatively small and are probably not significant from a therapeutic standpoint.

2. There is a marked and significant increase in the absorption of the insoluble tracer dye phenolsulfonphthalein through inflamed skin, most pronounced with eczematous dermatitis and much greater with polyethylene glycol as the vehicle (Base 1) than with white petrolatum. This increase may range to as high as 12 times greater absorption from the water-soluble base on eczematous skin than from the oleaginous vehicle on normal skin and suggests the possibility of the absorption of toxic amounts of certain drugs, even those relatively insoluble, if they are incorporated in washable vehicles in the concentration generally used in oleaginous ointments. This observation indicates the necessity of reducing the concentration of therapeutic agents.

3. This preliminary investigation presents many problems which will have to be solved in future studies. The following points are among those to be considered: (*a*) the differences in absorption of water-soluble substances from oleaginous and washable bases (by analogy to animal studies and to the work reported here, far greater absorption, especially through inflamed skin, is expected, particularly from the water-soluble bases); (*b*) the possibility of absorption of toxic quantities of soluble medicaments applied topically in washable bases; (*c*) the optimum concentrations for medications which can be employed in water-soluble bases with safety and yet satisfactory therapeutic results; (*d*) the potentialities of polyethylene glycol for cutaneous sensitization (in the present study no sensitization was encountered), and (*e*) the possibility that water-soluble bases, by promoting better penetration and absorption, may enhance the sensitizing power of drugs incorporated in them.

These points are the basis for continuing study by the authors, and the results will be reported in future publications.

KERATOSIS PUNCTATA PALMARIS ET PLANTARIS

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PUNCTATE keratosis of the palms and soles is a comparatively rare condition. The number of various names proposed by different authors nearly equals the total number of cases reported in the literature. Keratoderma disseminatum palmaris et plantaris, keratoma dissipatum hereditarium palmare et plantare, keratodermia maculosa disseminata palmaris et plantaris, punctate keratoses of palms of hands and soles of feet, and keratoderma punctatum are but a few of the titles selected. No unanimity has as yet been attained in regard to terminology.

Numerous cases with keratosis of the palms and soles have been recorded in the literature. A certain number of these, because of their identical physical and histological manifestations as well as their clinical course, fall into a distinct group, namely, keratosis punctata. The first recorded case of this anomaly was probably that of Davies-Colley in 1879. Subsequent publications have been presented by Galloway,[1] Sweitzer,[2] Leiberthal,[3] and Michael,[4] among others. The clinical, histological, and historical aspects are reviewed in the publications of Sweitzer and Lieberthal; Michael's article cites the hereditary aspects of this entity.

Keratosis punctata is characterized clinically by multiple discrete yellow to dark-brown, firm, slightly elevated, conical keratotic plugs varying from pinhead size to 0.3 cm. or slightly larger, occurring within normal skin. Removal of these firm, horny epithelial plugs results in the formation of small crateriform pits, which may be the initial factor in attracting the physician's attention to the disorder. Regrowth of these keratotic plugs within the pits begins at the apex of the remaining crater. The lesions are distributed rather symmetrically on the palms or soles, or both. The palmar aspects of the fingers and the plantar surfaces of the toes

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1. Galloway, J.: Punctate Keratoses of Palms of Hands and Soles of Feet, Brit. J. Dermat. **30**:123 (July-Sept.) 1918.

2. Sweitzer, S. E.: Keratoderma Punctatum, Arch. Dermat. & Syph. **8**:687 (Nov.) 1923.

3. Lieberthal, D.: Disseminated Palmar and Plantar Keratoderma, Arch. Dermat. & Syph. **14**:655 (Dec.) 1926.

4. Michael, J. C.: Keratoderma Disseminatum Palmaris et Plantaris: Its Mode of Inheritance, Arch. Dermat. & Syph. **27**:78 (Jan.) 1933.

comprise the only other sites affected. There are no subjective symptoms except in rare instances, when the lesions on certain areas may cause pain when pressure is applied (e. g., to the soles of the feet in walking). There is no coalescence or spontaneous desquamation of the lesions. A diffuse hyperkeratosis or scaling is not present. A gradual increase in the size or number of the lesions may occur. The disease usually makes its appearance near puberty, although the onset may occur during adult life, a few cases having been reported with their onset after 40 yr. of age. The condition apparently persists for life. Both familial and nonfamilial cases have been recorded. Of the familial cases, reports in the literature concerning the mode of inheritance indicate the condition is a dominant trait. Hereditary transmission has not been proved in all cases, however. Advocates of the hereditary theory of etiology suggest the following explanations in cases reported as nonfamilial:

1. The cast may represent an original mutation.

2. The condition may be transmitted by different modes of inheritance (other than dominant), so that generations may be skipped.

3. The patient may not know or be able to recall accurately whether other members of the family were afflicted.

The late onset of the disease has led others to believe it may be an acquired condition.

The histological features of this anomaly are characteristic. The major changes are in the stratum corneum. This layer is greatly hypertrophied in a circumscribed manner. The apex of this cone-shaped hyperkeratotic mass presses downward on the subjacent structures. At the surface this conical plug is loosely attached, but toward the apex it is more firmly fixed. The stratum lucidum may be slightly thinned. The stratum granulosum is essentially unchanged. The rete malpighii is normal except under the apex, where it may be compressed and the papillae obliterated. The individual cells show no pathologic changes. The stratum germinativum is intact, and there is no inflammatory infiltrate or other abnormalities in the corium. Parakeratosis, when present, is not considered to be an inherent feature of the lesion but rather the result of changes produced by trauma. Several authors have noted lesions occurring around sudoriparous ducts. These sweat ducts were elongated because of the thickened stratum corneum but were patent and normal in structure. However, this condition should not be referred to as a porokeratosis until further serial sections disclose more cases with periportal lesions. For this reason serial sectioning is advisable in all biopsies.

The following conditions, or their variants, have been mentioned in differential diagnosis: verrucae, arsenical keratosis, keratosis follicularis, porokeratosis Mibelli, angiokeratoma, keratoma plantare sulcatum, lichen planus, hyperkeratosis follicularis et parafollicularis in cutem penetrans, syphilis, yaws, psoriasis, and diffuse keratosis with punctae (punctate keratosis). The diagnosis should not be difficult in a true case of keratosis punctata. That these multiple, well-circumscribed keratotic plugs and crateriform pits are surrounded by entirely normal skin and that they are limited in distribution to the palmar and plantar surfaces are important differential factors. The familial tendency, futility of therapy, and the characteristic histological observations are additional factors. Generalized hyperkeratosis or erythema surrounding the individual lesions should not be present.

Fig. 1 (Case 1, T. B.).—Numerous discrete crateriform pits are present. Note the preponderance of lesions in the flexural folds.

Fig. 2 (Case 2, W. D.).—Numerous plantar lesions of various sizes are exhibited. Keratotic plugs are visible within some of the larger crateriform pits.

REPORT OF THREE CASES

CASE 1.—T. B., a 35-yr.-old Negro, was admitted to the dermatologic wards at Bellevue Hospital on Jan. 5, 1948. His chief complaint was two painful ulcerations of three weeks' duration located on his penis and left thigh, associated with an ipsolateral inguinal swelling. When questioned he stated the lesions on his palms and right sole were first noticed when he was 14 yr. of age. At that time he noticed small, hard, seedlike masses appearing on both

Fig. 3 (Case 1).—The skin and subcutaneous tissues reveal moderate acanthosis. A massive keratin plug fills a dilated hair follicle. There is mild thickening of the stratum granulosum.

palms. In time these lesions became large enough to be picked out, leaving minute depressions on his palms. New lesions would subsequently re-form in these pits. Gradually the lesions increased in number on the palms and also became noticeable on the sole of the right foot. The lesions were symptomless. To the best of the patient's knowledge none of his relatives had similar lesions. He was treated for latent syphilis in 1941 in Georgia, receiving an undetermined amount of bismuth and arsenical therapy. No serological tests for syphilis had been performed since this therapy.

Physical examination revealed numerous firm, dark-brown, elevated plugs, approximately 1 mm. in diameter, imbedded in normal skin. Numerous crateriform pits, also approximately 1 mm. in diameter and 0.75 mm. in depth, were present. Diffuse hyperkeratosis, hyperhidrosis, or other pathological features were not present on the hands or feet. There was no coalescence of the lesions. The only regions affected were the palms, palmar surfaces of the fingers, and the right sole. The palmar lesions were mainly located in or near the skin creases, with a symmetrical distribution. The penile lesion was located on the left lateral aspect of the penis. A similar lesion was also present on the proximal medial aspect of the left thigh in an area opposing the penile ulcer. Both lesions were circular, about 1 cm. in diameter, well-circumscribed ulcerations possessing undermined borders. Both were non-indurated, exquisitely

Fig. 4 (Case 3).—Left hand. Several keratotic plugs are visible along the flexural crease in the upper lateral quadrant of the palm.

tender, and covered with a purulent exudate. A tender bubo was present in the left inguinal region. The clinical diagnosis of these ulcers and the bubo was chancroid.

The results of urinalysis and blood counts were normal. The Ducrey intradermal antigen test gave a positive reaction, and the Frei antigen test, a negative one. The Mazzini and Kahn qualitative test reactions were 4+. The chancroid lesions healed promptly with sulfathiazole therapy.

Case 2.—W. D., a 27-yr.-old Negro, was admitted to the dermatologic wards at Bellevue Hospital on Feb. 26, 1948. His chief complaint was a penile sore of 10 days' duration. As in Case 1, the patient also presented lesions on his palms and soles. The plantar lesions appeared when the patient was approximately 20 yr. of age. His palmar lesions occurred only during

the past four years and were not as numerous as those on his soles. A gradual increase in their number occurred. After forceful removal, the firm horny plugs slowly recurred. No symptoms were associated with the palmar and plantar lesions. The patient stated that no other members of his family were similarly affected. His past history was otherwise irrelevant except for an admission to Bellevue Hospital in September, 1946: On that occasion he was treated for a seropositive penile chancre with 1,200,000 units of penicillin, 320 mg. of oxophenarsine hydrochloride (mapharsen®) and 0.6 gm. of bismuth. His serological reaction became negative after this therapy.

Physical examination disclosed numerous crateriform depressions and keratotic plugs similar to those described in Case 1. The lesions were sharply demarcated, being imbedded in normal

Fig. 5 (Case 3).—Right hand. Lesions may be noted along the flexural crease in the upper lateral quadrant of the palm. Note the symmetrical distribution on both palms (compare with Figure 4).

skin. The largest plantar lesions reached 2 mm. in diameter. Only the palms and soles and corresponding portions of the digits were involved. Coalescence of the lesions did not occur. No other pathologic changes were present on the hands or feet. A nontender, indurated ulceration 1.25 cm. in diameter on the distal right lateral aspect of the prepuce was noted. The clinical diagnosis of this lesion was primary syphilis.

The laboratory data were normal except for the positive results of the penile dark-field examination for Treponema pallidum and the positive serological reaction. Reactions to the Mazzini and Kahn qualitative test were 4+. The titer in the Kahn quantitative test was 8 units. No biopsy was performed. The antisyphilitic therapy consisted in the administration of

3,200,000 units of penicillin (40,000 units every three hours for 80 injections) and 0.6 gm. of metallic bismuth (0.12 gm. in five injections).

Three cases of keratosis punctata were observed by one of us (M. S.) among approximately 6,100 dermatologic cases seen at two United States Army general Hospitals. The palms of all patients were examined as part of the routine physical examination. The ratio for keratosis punctata in this series of cases was approximately 1 : 2,000. However, since the lesions of keratosis punctata are usually asymptomatic, it is reasonable to assume that the majority of persons with the condition do not seek medical consultation. Two of the three patients observed visited

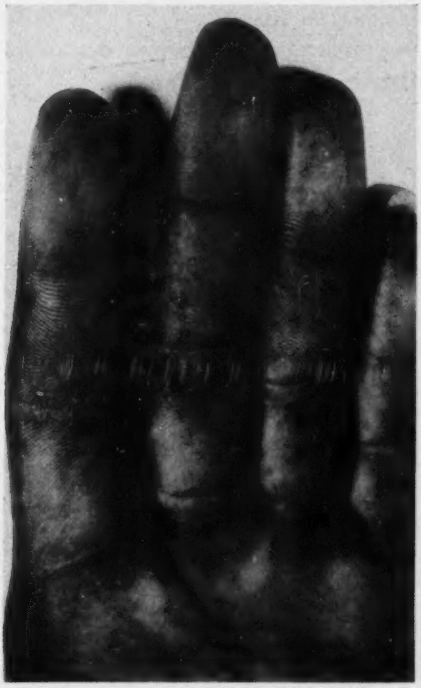

Fig. 6 (Case 3).—Left hand. A crateriform pit is visible at the junction of the proximal and middle phalanges of the middle finger. A healing biopsy wound is present at the junction of the distal and middle phalanges of the index finger.

the dermatology clinic complaining of the keratosis punctata lesions. The other patient was referred because of a nonrelated dermatitis, and keratosis punctata lesions were noted during the routine physical examination. Two patients were Caucasians; one was a Negro. One of the three cases will be described:

Case 3.—In July, 1948, a 30-yr.-old Negro soldier was seen in the dermatology clinic at William Beaumont United States Army General Hospital in El Paso, Texas. He stated that for the past one and one-half years he had noticed small "warts" appearing on the palms of both hands. These lesions were symptomless until they reached sufficient size to cause pain when pressure was applied. To relieve the symptoms the patient picked out the "warts." New

lesions subsequently formed in the holes which were left. There was no history of previous arsenical therapy. The patient had seven brothers (one older than he) and two sisters (both older), and none had a similar skin condition.

Several keratotic plugs and crateriform pits were present on both palms and palmar surfaces of several fingers. The lesions were mainly distributed in the flexural creases of the palms and fingers. No plantar lesions were present.

SUMMARY AND CONCLUSIONS

Cases of keratosis punctata palmaris et plantaris occurring in three patients are reported.

The condition is comparatively uncommon.

The histological features are reviewed.

The diseases to be considered in the differential diagnosis are listed.

140 East 54th St. (22).

OCCURRENCE OF MICROSPORUM GYPSEUM (M. FULVUM) INFECTIONS IN THE DISTRICT OF COLUMBIA AREA

Report of Six Cases

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INFECTIONS due to Microsporum gypseum (M. fulvum) have not been reported previously from the District of Columbia area. Indeed, there are few reports of its recognition as a causative agent of dermatophytosis in other sections of the United States. We have recently observed two patients with tinea capitis and four patients with tinea corporis from which M. gypseum was isolated.

REPORT OF CASES

CASE 1.—An 8-yr.-old boy was seen on Oct. 10, 1949, with a single inflammatory lesion of the scalp. It had appeared as a red, scaling area with partial alopecia and had been present for 10 days. The boy had been treated with hot compresses and parenteral administration of penicillin without improvement. Slight fever (99 F.) occurred early in the course.

Examination revealed a kerion, 5 by 7 cm. in diameter (Fig. 1). There was no fluorescence under Wood's light. A direct potassium hydroxide examination of an infected hair revealed an ectothrix fungus. M. gypseum was isolated by culture. Treatment with 5% ammoniated mercury ointment for three months resulted in recovery with return of normal hair. The source of the infection may have been a pet pony.

CASE 2.—A 3-yr.-old girl was seen on Oct. 4, 1950, because of an inflammatory lesion of the scalp. It had appeared one month previously as a small scaly patch, which gradually enlarged and was accompanied by falling hair. She had received no treatment. There were no apparent lesions on the patient's pet dog. Examination revealed a 4 by 5 cm., irregular, oval, impetiginous lesion on the left temporal region of the scalp with central alopecia and pustular border. There was no fluorescence under Wood's lamp. A potassium hydroxide examination of the infected hair revealed a fungus. M. gypseum was isolated by culture. Treatment with zinc undecylenate and a salicylanilide ointment resulted in uneventful recovery.

CASE 3.—A 7-yr.-old boy was referred on Aug. 16, 1949, because of an elevated, vesicular, previously exudative lesion 5 cm. in diameter on the right leg. The lesion had been present for several weeks. It had a granulomatous appearance when first seen and spread peripherally in spite of treatment with antiseptic ointment and penicillin administered parenterally. There was no known animal source. A direct potassium-hydroxide examination of scrapings from the lesion revealed a few fine hyphal strands. Cultures revealed M. gypseum. Recovery occurred after a three-month period of treatment with tincture of iodine and an undecylenic acid ointment.

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Identification of cultures from the cases presented was confirmed by Dr. Lucille K. Georg and Captain M. L. Littman, Medical Corps, United States Army.

CASE 4.—A 16-mo.-old girl was referred on Sept. 13, 1949, because of a 3 by 4 cm. scaling, slightly impetiginized lesion on the right leg of several months' duration. Topical application of various antibacterial agents had resulted in no improvement. Potassium-hydroxide examination revealed a positive reaction for hyphal strands. Culture revealed M. gypseum. A rapid and uneventful recovery followed applications of tincture of iodine and an undecylenic acid ointment.

CASE 5.—A 3½-yr.-old girl was seen on July 15, 1950, because of an annular, erythematous, scaling, papular lesion 3 cm. in diameter on the anterior lower leg. It had been present for seven days. Treatment with an undecylenic acid ointment for one week had resulted in no response. A direct potassium hydroxide examination gave positive results. Culture revealed M. gypseum. A similar lesion appeared later on the buttocks. Both lesions resolved after three-weeks' treatment with a benzoic and salicylic acid ointment. M. gypseum was also cultured from a lesion on the patient's cat.

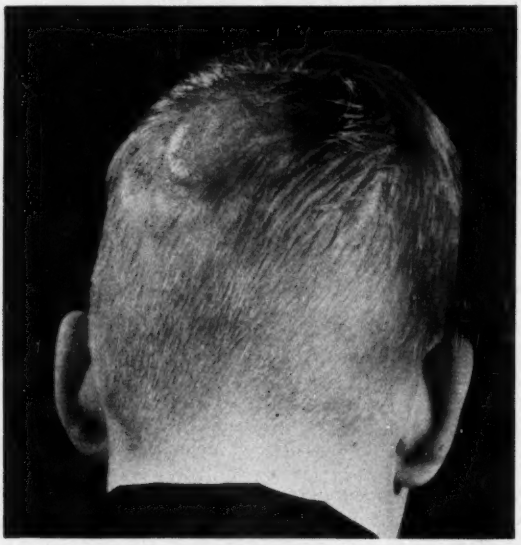

Fig. 1 (Case 1).—Kerion of scalp due to Microsporum gypseum.

CASE 6.—A 57-yr.-old woman was seen on Aug. 25, 1950, because of an annular, erythematous, crusted lesion, 2 cm. in diameter on the upper abdomen. The border was raised, vesicular, and slightly exudative. It had appeared 5 days previously after contact with pet dogs. The dogs were not available for examination. A potassium hydroxide examination disclosed numerous hyphal strands. M. gypseum was isolated by culture. Healing occurred in three weeks following treatment with a zinc-oxide paste during the acute stage, benzoic and salicylic acid ointment, and several applications of a chrysarobin solution.

MYCOLOGIC CHARACTERISTICS

Cultures from the six patients were isolated on Littman's oxgall agar [1] and transferred to Sabouraud's glucose agar for identification. Typical colonies appeared within seven to 10 days. The surface growth appeared first as white, woolly, circular

1. Littman, M. L.: A Culture Medium for the Primary Isolation of Fungi, Science **106**:109 (Aug. 1) 1947.

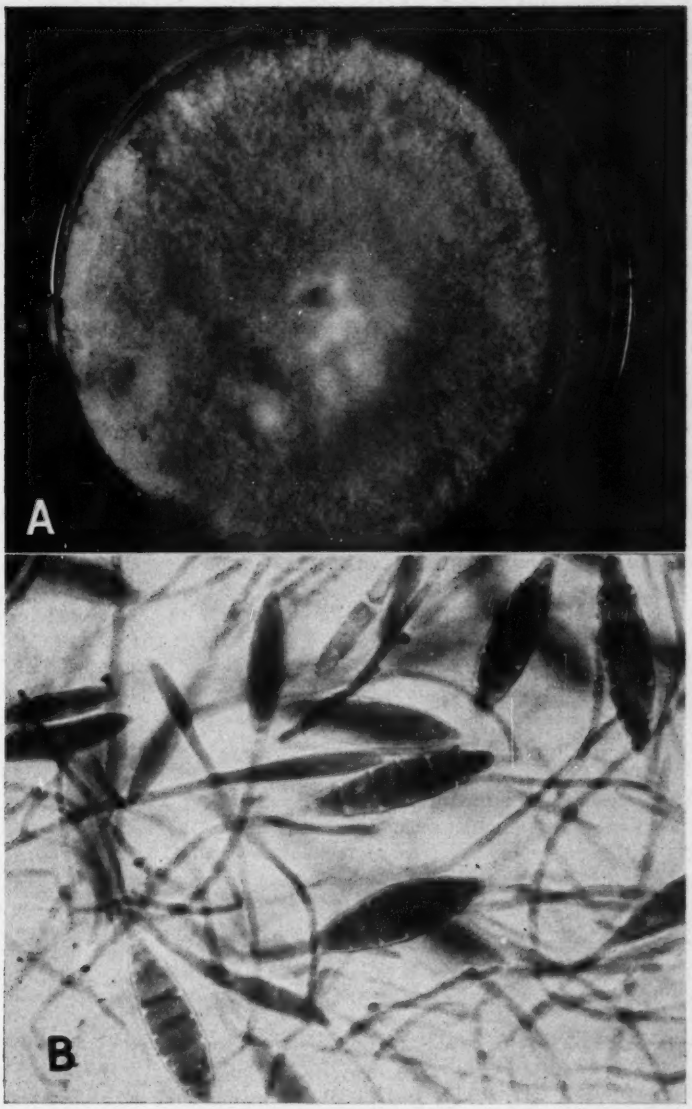

Fig. 2.—*A*, colony of M. gypseum on Sabouraud's glucose agar; a transplant after 15 days. *B*, morphologic characteristics of M. gypseum (with lactophenol cotton blue stain).

colonies which soon developed a buff-to-cinnamon-tan, granular appearance with a tiny central umbo (Fig. 2*A*). Fine pale radiating furrows developed on the periphery. White fluffy areas of pleomorphism developed in old colonies. Reverse of the colonies on Sabouraud's glucose agar was at first yellow-orange and later darkened to red-brown in old cultures. All specimens grew rapidly on rice media.

Microscopic examination showed a profusion of large, ellipsoid, moderately rough-walled macroconidia with from three to six septations (Fig. 2*B*). There were a few clavate microconidia and chlamydospores.

COMMENT

M. gypseum was first isolated in this country in the New York area,[2] and early cases were observed only among immigrants from Latin America. Infection due to this organism has received only scant recognition in medical literature. However, recent surveys of tinea capitis have included scattered cases due to M. gypseum. In a study of 130 cases of tinea capitis in the Philadelphia area, Livingood and Pillsbury [3] reported only one case due to M. gypseum. Lewis and Hopper [4] isolated six from 456 cases in the New York area. Benedek and Felsher [5] found only three among 140 cases reported from Chicago. Lehmann, Pipkin and Ressmann,[6] reporting the cultural findings in 170 cases in San Antonio, found M. gypseum six times. Sharp and Wegner [7] have recently called attention to M. gypseum as an etiologic agent of dermatophytosis in this country and reported eight cases from Galveston.

As a cause of tinea corporis M. gypseum has received less attention. The four patients whose cases are presented here showed marked inflammatory reaction, three having been treated by the referring physicians with antibiotics for "impetigo." The lesions had the usual characteristics of fungus infections of animal origin, except that the inflammatory reactions seemed uniformly more intense and prolonged, and in one patient approached a granulomatous appearance. All responded to relatively simple antifungal therapy. The isolation of M. gypseum by culture, therefore, would seem to have no prognostic significance other than to classify the infection.

M. gypseum was cultured from the pet of one patient, and animals may have been the source of infection in some of the other cases. All patients were residents of this urban area; none had been out of the continental United States. It was of interest that, although Microsporum infections are considered rare in adults, one of our patients (Case 5) was 57 yr. old.

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2. Emmons, C. W.: Observations on Achorion Gypseum, Mycologia **23**:87 (March) 1931.

3. Livingood, C. S., and Pillsbury, D. M.: Ringworm of the Scalp: Prolonged Observation, Family Investigation, Cultural and Immunologic Studies in 130 Cases, J. Invest. Dermat. **4**:43 (Feb.) 1941.

4. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, ed. 3, Chicago, The Year Book Publishers, Inc., 1948.

5. Benedek, T., and Felsher, I. M.: Epidemiology of Tinea Capitis, Arch. Dermat. & Syph. **49**:120 (Feb.) 1944.

6. Lehman, C. F.; Pipkin, J. L., and Ressmann, A. C.: Cultural Survey of Tinea Capitis in San Antonio, Texas, Arch. Dermat. & Syph. **61**:488 (March) 1950.

7. Sharp, W. B., and Wegner, M. J.: Microsporum Gypseum as an Etiologic Agent in the United States, Arch. Dermat. & Syph. **61**:824 (May) 1950.

Conant,[8] who has identified M. gypseum four times from cultures taken from patients in the Durham area in the past several years, believes that the species is being found more frequently now than previously. It is difficult to determine whether this increase in frequency of observation of the organism is a true or relative increase in incidence, since fungus cultures are being done more routinely.

SUMMARY AND CONCLUSIONS

Dermatophytosis due to Microsporum gypseum has not been reported previously from the District of Columbia area. Two cases of tinea capitis and four cases of tinea corporis due to M. gypseum are presented. An intense inflammatory reaction was characteristic of these cases. Relatively simple antifungal therapy produced uneventful resolution in all cases.

The incidence of infections due to M. gypseum is increasing in the continental United States. Apparently these infections are originating endemically rather than in the Latin-American countries as was formerly observed.

ADDENDA

Since submission of this report for publication, three additional cases of infection due to Microsporum gypseum have been seen. Two children had tinea capitis, only one of which showed fluorescence; another child had tinea corporis.

Variations in fluorescence have been described in two additional reports published recently.[9]

Walter Reed General Hospital (Captain Trice).
1007 N. Highland St. (Dr. Shafer).

8. Conant, N. F.: Personal communication to the authors.

9. Dalton, J. E.; Slaughter, J. C.; Jenkins, R. E.; Phelps, S., and Hackney, V. C.: Microsporosis due to Microsporum Fulvum, J. Invest. Dermat. **15**:421 (Dec.) 1950. Wilson, J. W., and Plunckett, O. A.: Lack of Fluorescence of Scalp Hairs Infected With Microsporum Gypseum (Fulvum), ibid. **16**:119 (March) 1951.

HYPERTROPHIC LICHEN PLANUS IN WEST AFRICAN NEGROES

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LAGOS, NIGERIA

DURING the war of 1939 to 1945, a large number of papers were written on the appearance of a lichen-planus-like disease among white troops in the tropics who had been taking quinacrine. That quinacrine is concerned in the etiology there can be no doubt.[1] What is the precise mechanism, however, is open to different interpretations. It is usually assumed to be a toxic or allergic manifestation following treatment with quinacrine, i. e., a drug eruption, but equally quinacrine could act as a trigger factor in activating a lichen-planus-like disease endemic to the tropics, as fever may activate herpes febrilis or arsenic activate herpes zoster.

Whatever the explanation, a disease resembling lichen planus hypertrophicus and which I believe in fact to be this disease is relatively common among the Negroes of southern Nigeria. The picture is striking and characteristic and has not, so far as I am aware, been commented on. This fact is surprising in view of the relative rarity of the condition in Europe. Presumably the disease is part of the group reported as lichenoid eruptions.[2]

DESCRIPTION

The rash, which may be present over the whole body, is more usually confined to the legs. It is almost invariably symmetrical. It consists of large, flat, raised plaques with or without smaller papular lesions. Sometimes the eruption is confined to a few large plaques. These are of two main types. Those of the first approximate the classic violaceous, flat-topped, shiny polygonal papules of lichen planus (Fig. 1), and the smaller accompanying papules are invariably of this nature. In the second type the lesions are rather more raised and infiltrated, even nodular, being deep black but often depigmented in the center and exhibiting a curious pitted or honeycomb-like appearance (Fig. 2). They never ulcerate.

The disease is often stationary and of long duration (years) but may develop quite quickly (weeks). Both sexes are affected, but males were more commonly seen with the disorder. The itching is intense and brings the patient to request

*Dermatologist, Nigerian Medical Service.

1. Sulzberger, M. B., and Baer, R. L.: 1944 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1945, p. 30. Clarke, G. H. V.: A Case of Mepacrine Dermatitis, Brit. M. J. **2**:58 (July 9) 1949.

2. Foerster, H. R., in discussion on Nomland, R.: A Case for Diagnosis (Prurigo Mitis in a Negro?); Dermatosis Papulosa Nigra, Arch. Dermat. & Syph. **22**:187 (July) 1930. Loewenthal, L. J. A.: Diseases of the Skin in Negroes, J. Trop. Med. **39**:277 (Dec.) 1936.

treatment, to which, however, the condition is very resistant. The blood serologic reaction is almost invariably negative. Associated hypochromic anemia was sometimes noticed, but its presence was probably a coincidence. Of the 27 patients examined none was tuberculous.

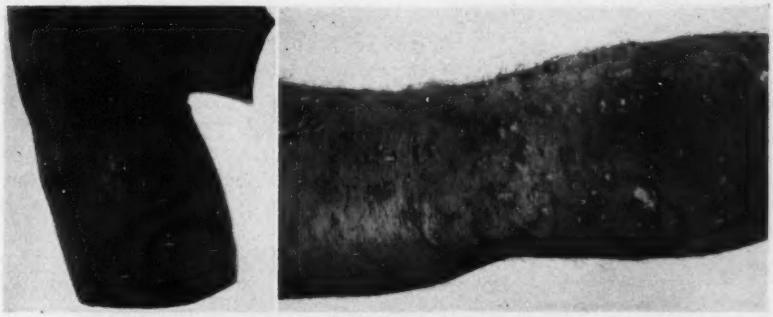

Fig. 1.—The classic violaceous, flat-topped, shiny polygonal papules which constitute one type of rash found in hypertrophic lichen planus in West African Negroes.

Fig. 2.—The second kind of eruption found in hypertrophic lichen planus in West African Negroes; the lesions, which are more raised and infiltrated, even nodular, are deep black, often with central depigmentation, and exhibit a curious pitted or honeycomb-like appearance.

HISTOLOGICAL PICTURE

Both types exhibit the same microscopical appearance in section (Figs. 3 and 4), which is that of lichen planus hypertrophicus. A typical biopsy report is as follows:

The epidermis is thickened and verrucose over a circumscribed area. There is acanthosis and hyperkeratosis, and the epidermis is raised in broad papillary folds with horny plugs between them. In the dermis there is a dense infiltration of small round cells in the papillary and subpapillary layers; this infiltration is sharply limited to the superficial part of the dermis and ceases abruptly at the edge of the lesion.

The histologic picture is typical of lichen ruber verrucosus.

DIFFERENTIAL DIAGNOSIS

Several other conditions have to be eliminated before one may assume that the lesions are in fact hypertrophic lichen planus.

Syphilis.—The almost invariably negative serologic reaction is against the diagnosis of syphilis, while the extremely poor response to arsenic, bismuth, or mercury therapy is almost conclusive. In one case 27 bismuth injections were given, with no improvement.

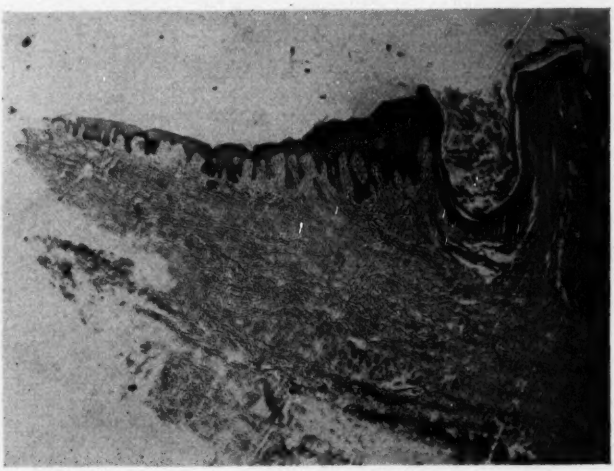

Fig. 3.—Photomicrograph of a section of a biopsy specimen, showing the histological picture of lichen planus hypertrophicus.

Amyloidosis.—Amyloidosis of the skin is often confused with lichen planus.[3] It can be diagnosed only by specific staining for amyloid with methylrosaniline chloride or congo red. In the cases studied amyloid was never found.

Lichenified Dermatitis or Eczema.—Lichenified dermatitis or eczema might show a similar appearance in certain areas but would also show areas more typical of these conditions. There would also probably be evidence of some chronic irritant. No irritant was ever discovered. In any case, the Negro skin is resistant to irritants. And, finally, the histological picture is not that of eczema.

Neurodermatitis.—Neurodermatitis might show a lichenified patch similar to one of the large plaques, but hardly multiple patches. None of the patients appeared to be of the "neurotic" type.

3. Freudenthal, W.: Amyloid in der Haut, Arch. Dermat. u. Syph. **162**:40, 1930. Freudenthal, W., and Dowling, G. B.: Lichen Amyloidosis, Proc. Roy. Soc. Med. **32**:1029 (July) 1939.

Psoriasis.—Psoriasis is very rare indeed in the Negro. The clinical and histological appearances rule out psoriasis.

Quinacrine Dermatitis.—Some of the patients had taken quinacrine, but none regularly or in large doses. There was no time correlation, and most of the patients had never taken the drug.

Chromoblastomycosis.—No fungi were ever found.

Tuberculosis Verrucosa Cutis.—The histological picture rules out tuberculosis verrucosa cutis.

Leishmaniasis.—No Leishman-Donovan bodies were ever found.

Prurigo Nodularis.—Some of the cases would fit the description of prurigo nodularis, and the biopsy picture would not absolutely rule it out. On the other hand, the occurrence of mixed cases with typical lichen planus papules and the relatively high incidence are against this diagnosis.

Fig. 4.—Photomicrograph of a section of a biopsy specimen, showing the histological picture of lichen planus hypertrophicus.

TREATMENT

As stated above, the disease is extremely resistant to treatment with arsenic, bismuth, or mercury preparations, all of which are often effective in the ordinary type of lichen planus. Local application of tar proved valueless.

It was noted that individual plaques from which biopsy specimens were removed always healed in their entirety. Various local destructive measures were then tried, including application of nitric acid and of phenol, scraping, application of 30% salicylic acid, use of the cautery, and local injection of chaulmoogra oil. These procedures were frequently successful, but unfortunately this success was usually only temporary and the lesions tended to recur. The areas which had furnished biopsy specimens, however, never had recurrence.

TRANSPLANTATION EXPERIMENTS

An attempt was made to see whether the disease were a local one or depended on the area affected. Haxthausen [4] carried out transplantation experiments in vitiligo and found that the normal skin transplanted to the affected area became diseased, while the diseased skin transplanted to a normal area became normal. Thus vitiligo is a place disease, perhaps mediated by the nerve supplying the part. A similar result was obtained in fixed eruptions by Wise and Sulzberger.[5] On the other hand, Haxthausen [4] found that psoriasis when transplanted flourished in its new site and thus must be a local disease, which observation would point to the presence of an infection.

Procedure.—The following procedure was adopted in the present cases. An area of normal skin the same size as one of the plaques was cut out to make a bed for the plaque. The plaque itself was then excised and moved to this bed while the normal skin was put in its place. Another but smaller area of normal skin was excised and the wound left open to see whether the Köbner phenomenon would occur. If it did occur it would vitiate the results. It was not, however, observed in any of the patients operated upon.

Results.—In most cases the grafts did not take and all the areas healed as normal skin. In two cases, however, a successful transplantation took place and the lichen planus plaque did survive in its new site, but after about two months it disappeared, leaving normal skin. Presumably the inflammation incidental to the transplantation acted, like that accompanying the removal of the biopsy specimens, as a healing stimulus. Equally important, the normal skin transplanted into the lichen planus site survived as normal skin.

These results point to a local cause, possibly a virus infection, and to the conclusion that lichen planus is a local disease like psoriasis.

COMMENTS

The etiology of lichen planus is unknown. Several facts, however, point to the possibility of an infection, as in the cases reported by Barber.[6]

The hypothesis of a virus etiology would fit in with the results of transplantation experiments, and it would be comprehensible that the disease could be activated by trauma, nervous shock, the use of quinacrine, focal infections, etc.

Lichen planus has been stated to be rare in the Negro.[7] The present condition is not excessively rare, cases of it constituting 1.1% of all skin diseases seen in Lagos.

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4. Haxthausen, H.: Studies on Pathogenesis of Morphea, Vitiligo and Acrodermatitis Atrophicans by Means of Transplantation Experiments, Acta dermat.-venereol. **27**:352, 1947.

5. Wise, F., and Sulzberger, M. B.: Drug Eruptions: Fixed Phenolphthalein Eruptions, Arch. Dermat. & Syph. **27**:549 (April) 1933.

6. Barber, cited by Sequeira, J. H.; Ingram, J. T., and Brain, R. T.: Diseases of the Skin, ed. 5, London, J. & A. Churchill, Ltd., 1947.

7. Winer, L. H., and Levitt, H.: Lichen Planus in the Negro, Arch. Dermat. & Syph. **56**:437 (Oct.) 1947.

SUMMARY

A disease thought to be lichen planus hypertrophicus appears to be relatively common in West African Negroes. Other possible diagnoses, such as quinacrine or amyloid dermatoses, have been eliminated. Some transplantation experiments are described, and the results are in agreement with a virus causation. Local treatment is temporarily effective, and systemic treatment with arsenic, bismuth, or mercury preparations, useless.

Mr. Kent of the pathology department took the photographs; Dr. J. D. Manning made the histological report, and Dr. G. B. Walker, C.B.E., D.M.S. Nigeria, gave me permission to publish this paper.

SUCCESSFUL TREATMENT OF PEMPHIGUS WITH HEPARIN

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R. CAMPBELL MANSON, M.D.
AND
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THE PURPOSE of this paper is to present observations suggesting that heparin possesses the ability to induce a remission in pemphigus.

This disease, of unknown etiology, was first described in medical writings of the 17th century. Prior to that time there were no descriptions of disease states which might be interpreted as consistent with it.[1] At present four varieties of pemphigus are recognized: pemphigus vulgaris, the common form of the disease; pemphigus foliaceus; pemphigus vegetans, and erythematoid benign pemphigus (Senear-Usher syndrome). The acute pemphigus of butchers is now considered to be a fulminating rapidly fatal bacteremia, while pemphigus neonatorum is considered to be bullous impetigo.

Pemphigus vulgaris is characterized by the development of successive crops of bullae, irregularly bilateral in distribution, usually erupting on normal-appearing skin or mucous membranes. At first the bullae contain clear serous fluid and are not surrounded by an inflammatory areola but later (24 hr. to a few days) the contained fluid becomes turbid and an inflammatory areola appears. In many cases there is a so-called "primary" lesion consisting of a moist eczematous patch usually on the scalp, the umbilical region, or the axilla. It is quite resistant to treatment, and its significance is not appreciated until crops of bullae appear elsewhere. Though the disease is characterized by remissions and relapses, the usual termination is fatal, with eventual prostration and death through intercurrent infection or debility.

Pemphigus foliaceus is a less common and more chronic form of the disease which tends to resemble exfoliative dermatitis.

Pemphigus vegetans is characterized by development of papillomatous and vegetating lesions superimposed on the bullae of ordinary pemphigus (vulgaris). These lesions usually form in the moist sweaty areas, such as the groins and axillae. It is rare and may possibly be due to secondary infection.

Presented before the staff, Medical College of Virginia, on May 12, 1950.

From the Medical Service, McGuire Veterans Administration Hospital, and the Department of Dermatology, Medical College of Virginia.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Rattner, H.: Med. Clin. North America **33**:165-176 (Jan.) 1949.

In the classification of erythematoid benign pemphigus (Senear-Usher syndrome) are a group of cases the initial lesions of which, though bullous, resemble lupus erythematosus by distribution in butterfly pattern across the nose together with a seborrhea-like dermatitis of the trunk. Their clinical course is prolonged, with frequent remissions and exacerbations, but most patients eventually manifest typical fatal pemphigus vulgaris.

Diagnosis of pemphigus is based on the appearance of the individual early lesions in which there is no zone of inflammation or induration, as in erythema multiforme (bullosum); no combination of vesicles, papules and pustules, as in dermatitis herpitiformis, and no evidence of infection, as in impetigo. Drug eruption is ruled out by history and by withdrawal of the noxious agent. In addition, many cases of pemphigus are characterized by the ease with which normal-appearing epidermis may be avulsed in response to pinching or rubbing (Nikolsky's sign).

The microscopic appearance of the lesion of pemphigus is not pathognomonic of the disease in that occasional lesions of other diseases may resemble it. Generally, however, a bulla or bleb is situated between the superficial and the deep layers of the epidermis or at the dermis-epidermis junction superficial to the rete pegs. There is little or no inflammatory reaction, but in the underlying dermis the collagen tissue may have the glassy appearance of degenerative disease. In impetigo the vesicle is just beneath the stratum corneum and is associated with considerable inflammatory reaction. The site of the bulla in dermatitis herpitiformis and erythema multiforme is beneath the epidermis. In the hereditary affliction, epidermolysis bullosa, the tissue separation may occur in the deep part of the epidermis or in the dermis (corium). In the latter disease, trauma to the skin is a supplemental factor in the development of its lesions.[2]

Consideration of this factor in a condition wherein there is presumably a hereditary defect in "cement substance" caused us to speculate on the probability of an acquired but identical defect in pemphigus. Knowing very little concerning "cement substance," we borrow from those doing investigational work in rheumatic diseases. Their studies indicate that all connective tissue is composed of interfibrillar substances and fibrillar material. Of the former, two components are distinguished, the amorphous and viscous ground substance and the cement substance proper. While the complete chemistry of these components is not known, hyaluronic acid and chondroitin sulfates (acetylgalactosamine sulfate and uronic acid) have been isolated.[3]

Both of these isolated mucopolysaccharides are inactivated by the enzyme hyaluronidase, which normally is found only in the testes.[4] These mucopolysaccharides or their component parts have been isolated from skin as well as other tissues.[5] Investigators have noted that the administration of hyaluronidase can

2. Percival, G. H.; Drennan, A. M., and Dodds, T. C.: Atlas of Histopathology of Skin, Baltimore, William Wood and Company, 1947, pp. 139-141.

3. Meyer, K., and Ragan, C.: Mod. Concepts Cardiovas. Dis. **17**:[N. P.] (Feb.) 1948.

4. Schwartzman, J.; Henderson, H., and King, W.: J. Pediat. **33**:267-273 (Sept.) 1948.

5. Pemberton, R., and Kelchner, C. in: Piersol, G. M.: Cyclopedia of Medicine, Surgery, and Specialties, F. A. Davis, Service Edition 213-214, 1949.

simulate a rheumatic disease or can cause a relapse of a quiescent rheumatic disease.[6] Bullae have been produced by the intradermal injection of hyaluronidase.[7]

On the theoretical basis that an acquired defect in pemphigus might be an analogue to the induced defect in experimental rheumatic diseases, the therapeutic use in pemphigus of a substance which inhibited the action of hyaluronidase was weighed. Of such substances the following were considered: flavones, gentisuric acid salts, heparin, crude vitamin C, corticotrophin (ACTH) and cortisone.[8] Because of its availability in a form for parenteral administration, heparin was chosen as the agent for therapeutic trial.

Heparin is a clot-inhibitor believed to originate in the mast cells of Ehrlich, having the general composition of mucoitin-poly-sulfuric-esters (i. e. complex carbohydrate derivatives), the molecular building stones of which are: glycuronic acid, glucosamine, acetic acid (?), and sulfuric acid (ester linked).[9]

REPORT OF A CASE

Briefly summarized is a report of a case in which the diagnosis of pemphigus was concurred in by our dermatology staff. Because a single case is presented, the follow-up period short, and the disease remarkably characterized by the occurrence of remissions, this communication must be considered preliminary in the strictest sense of the word.

M. A., a 30-yr.-old butcher of Jewish extraction, was admitted to the hospital on Sept. 26, 1949, by transfer. At the time of this admission, the patient had a bullous eruption of six weeks' duration involving the skin of the scalp, the face, the neck, the anterior part of the chest, the back, and the mucous membrane of the nose, mouth, and tongue as well as the perianal region. The onset of the illness was established as six weeks prior to this admission, at which time the patient underwent a surgical procedure for correction of a deviated nasal septum, after which he noted the appearance of vesicular lesions in the left temporal region. Within a week this eruption spread to involve the areas specified above. Parenthetically, the report on the physical examination recorded by the intern before operation noted but did not describe a skin lesion in the region of the left ear.

Therapy during the six weeks prior to the present admission consisted in local applications of penicillin, tyrothricin, and two or three mercurial preparations. In addition, the patient received penicillin parenterally and aureomycin hydrochloride orally in acceptable doses for two weeks. Borrelidin (an antibiotic prepared from soil mold, said to be effective against Borrelia nonyi) was also given by the intravenous route, and bacitracin ointment had been used for the two days just prior to admission. The patient's past history was not enlightening except for the occurrence of ruptured tympanic membranes from blast concussion in 1942 and two periods of hospitalization for "blood poisoning" arising from paronychia incurred during work as a poultry dresser while in military service in the years 1943 and 1945, respectively.

At the time of admission to McGuire Hospital (Sept. 26, 1949) the patient weighed 235 lb. (107.5 kg.), was afebrile, and had no symptoms other than pain and discomfort from his mucous-membrane lesions. The initial laboratory studies revealed nothing of significance with the exception of 11% eosinophiles in the differential white cell count.

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6. Seifter, J. (Wyeth Institute of Applied Biochemistry): Personal communication to the author, 1949. Jaworski, A. A., and Farley, J. E.: Hyaluronidase in Administration of Fluids, Am. J. Dis. Child. **79**:59-64 (Jan.) 1950.

7. Grais, M. L.: J. Invest. Dermat. **13**:221-222 (Nov.) 1949.

8. Beiler, J. M., and Martin, G. J.: J. Biol. Chem. **171**:507-511 (Dec.) 1947. Levitan, B. A.: New England J. Med. **241**:780-789 (Nov. 17) 1949. Alburn, H. E.: Address read before the Philadelphia Rheumatic Society, Feb. 24, 1949.

9. Jorpes, J. E.: Heparin: Its Chemistry, Physiology and Application in Medicine, London, Oxford University Press, 1939. Ferguson, J. H.: Ann. New York Acad. Sc. **49**:486-500 (May 11) 1948.

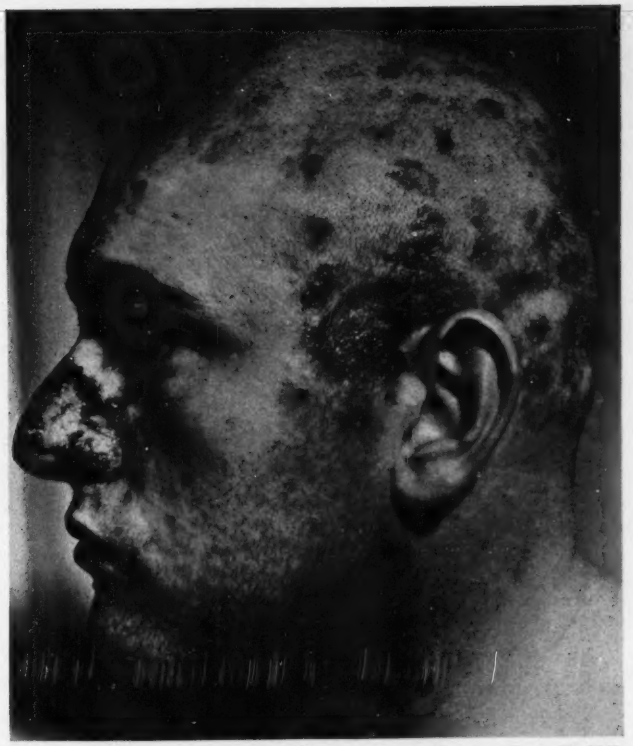

Fig. 1.—Bullous eruption on the third day of hospitalization, Sept. 28, 1949.

Fig. 2.—Eruption on the feet on Nov. 4, 1949.

Therapy during the first five months of hospitalization consisted in the use of a multiplicity of topical and systemic medications, including bacitracin ointment to the lesions twice daily,

Fig. 3.—Pemphigus eruption on the body on Nov. 21, 1949.

Fig. 4.—Pemphigus eruption on the hands on Nov. 21, 1949.

boric-acid compresses, petrolatum-gauze dressings, chloresium® ointment (containing the purified therapeutically active, water-soluble derivatives of chlorophyll "a"), methylrosaniline chloride and cottonseed oil, and topical anesthesia to the buccal mucosa before meals, penicillin given

intramuscularly, and borrelidin and suramin (naphuride®) sodium administered intravenously as well as extensive trial of chloramphenicol (chloromycetin®) and aureomycin. In addition, 300 r x-rays in four divided doses were given to the upper part of the abdomen over the hepatic and splenic regions. A high-protein diet was maintained throughout the treatment period; supplemental vitamins were given parenterally, and a total of 7,500 cc. of whole blood was administered.

During this time the patient ran a basically febrile course, weight dropped to 118 lb. (53.5 kg.), hemoglobin to 9.6 gm., and serum protein to 3.3 gm., with 1.6 gm. of albumin and 1.7 gm. of

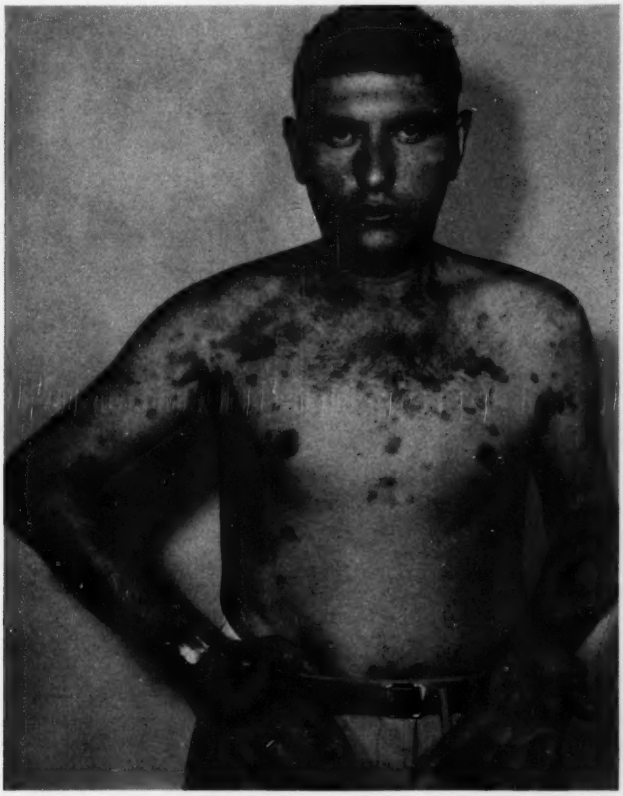

Fig. 5.—Results of therapy at the time of the last follow-up examination, April 18, 1950.

globulin. The patient had recurrent periods when he was better systemically as well as from the standpoint of skin lesions, but most of these improvement periods were like a brief intermission between eruptions of successive crops of skin lesions.

In mid-February heparin sodium (Abbott) was applied twice daily to the antecubital area of the right arm as a test to ascertain whether or not hemorrhagic manifestations might result from its use. This was continued for several days, during which time another crop of bullae appeared, involving the lumbar region, the abdomen and all extremities, but there was no increased tendency towards hemorrhage. On Feb. 24 intramuscular administration of delayed-absorption type heparin (Depo-Heparin,® The Upjohn Company, Kalamazoo, Mich.) was begun

with a dose of 200 mg. daily, the coagulation time during 20 days of therapy ranging from 10 to 43 min. Within four days practically all lesions had disappeared. The patient became ambulatory; his appetite became voracious. Heparin was continued until March 15, at which time the last break in the skin was closed. The patient was discharged from the hospital on March 20 and was followed as an outpatient since that time. There was a progressive gain in weight up to 180 lb. (81.6 kg.) at the time of writing (May 11, 1950). No new lesions had appeared. The pigment changes of the skin were gradually regressing, and the patient was indulging in unrestricted normal activity.

Fig. 6.—Condition of the feet on April 18, 1950.

CONCLUSIONS

The dramatic improvement following institution of therapy instills hope that an induced rather than a spontaneous remission was observed. If this is true, we are yet uncertain of the mechanisms involved in obtaining the result. Whether the administration of heparin in itself brought about correction of the "cement-substance" defect or whether the improvement was due to an interrelation between superficial application followed by parenteral administration will not be clear until more cases are observed.

USE OF THE HYPOSPRAY® IN DERMATOLOGY

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THE HOLLOW needle for injections has been used in medicine without many essential modifications for years. Some five years ago an experimental injector apparatus was devised which made use of spring-activated plungers and no needle. For the past two years, the Department of Dermatology of the College of Medicine of the University of Cincinnati has been interested in the adaptation of various modifications of this apparatus, called the hypospray,® in clinical and investigative dermatology. The project was assigned first to Thompson, who worked with Larrick.[1] They reported their initial clinical and investigative experiments on dermatologic patients. Because of the availability of lesions of the skin, this apparatus appeared to be of value for local therapy and also for use in systemic therapy. The present report is a critical summary of our investigative and clinical experiences with recent adaptations of this instrument.

The instrument is, briefly, a metal apparatus with spring-activated plungers. The pressure from these plungers forces out a sterile solution from a tiny orifice in a metal ampule called a metapule.® The ejected fluid is in the form of a fine spray which travels at tremendous velocity. This material pierces the skin, and its depth of penetration is controlled by spring pressure. In our studies, the pressure has been designated in terms of markings on the instrument. *A* is maximum pressure, with *1A, 2A, 3A,* etc., representing relative decreases in the spring pressure. For example, *1A* is obtained by moving the spring back one complete reverse turn; *2A*, by moving the spring back two turns, etc. The volume of material can also be regulated from 1.0 cc. down to 0.6 cc.

The basic anatomical and physical studies with the instrument were performed by Figge.[2] The necessity for tracing the course of the injected material through

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Various hypospray® models and metapules® were furnished by J. M. McKibbin, R. P. Scherer Corporation, Detroit.

From the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati, Dr. Leon Goldman, director.

Read before the Section on Dermatology and Syphilology at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 30, 1950.

1. Larrick, L. E., and Thompson, R. G.: The Hypospray and Its Relationship to Dermatology: Preliminary Report, J. Invest. Dermat. **13**:361-370, 1949. Thompson, R. G.; Larrick, L. E., and Preston, R. H.: Hypospray Technics in Dermatology, Exhibit, American Academy of Dermatology and Syphilology, Chicago, December, 1949.

2. Figge, F. H. J., and Scherer, R. P.: Anatomical Studies on Jet Penetration of Human Skin for Subcutaneous Medication Without the Use of Needles, Anat. Rec. **97**:335, 1947.

normal and pathologic skin soon became apparent. Previous tracer substances studied had been colored solutions, colloidal suspensions, colored oils, and metallic mercury. The penetration of all these was studied in cadavers. Later, iodopyracet injection (diodrast*) was employed with living subjects. We have found trypan blue and fluorescein useful in studying the pattern of distribution both in portions of excised skin and in vital staining of the skin of patients. To trace deep injections iodopyracet injection was used in five patients. In addition, biopsy specimens were obtained from areas injected with saline solution and procaine hydrochloride solution.

One per cent trypan blue and 0.1% sodium fluorescein were the most practical tracer aids. In most patients there was initial burning and pain with the injection (pressures *3A* and *3C*). The course of the injection was studied as follows: by gross examination of the skin, by direct cutaneous microscopy of the surface of the skin, both after injection and after biopsy, and, lastly, by study of prepared histological sections stained with trypan blue. Fluorescein was observed grossly in excised tissue on examination of the tissue under ultraviolet light with the use of a Wood filter. We preferred the skin of patients to postmortem (3 to 11 hr.) skin.

With these tracer substances we have shown that the depth of penetration and lateral distribution (breadth) of injected substances depends on (1) the spring pressure of the instrument, (2) the angle of the instrument with regard to the surface of the skin, (3) the pressure with which the instrument is held against the surface of the skin, (4) the type of applicator tip on the instrument, and (5) the basic character of the skin as regards such factors as thickness and pathologic involvement.

It became apparent from our early experiments that for the hypospray® to be of value in topical dermatologic therapy a relatively greater proportion of the medication must be deposited in the superficial portion of the skin. The tracer and clinical experiments revealed that this type of distribution could be accomplished by (1) reducing the spring pressure, (2) increasing the width of the injection stream, and (3) increasing "resistance" of the superficial tissues. To accomplish these purposes in our initial experiments, we used a rubber sponge about the injection site. Later, special rubber tips fixed to the instrument produced more adequate superficial injections. Moreover, plans have been outlined to use radioactive tracers in a technic for studying distribution and especially for evidence of involvement of blood vessels.

Sodium fluorescein has been used to study the possibilities of contamination of the skin surface, the apparatus, and the fingers of the operator by the injection. This point is of importance in the use of highly sensitizing materials such as penicillin and procaine. It was found that tight pressure with the applicator tip limited contamination of the skin surface to a small area about the site of injection. Contamination of the instrument is limited to the applicator tip. However, because of the relatively large size of the particles, superficial injection of aqueous suspensions of penicillin produces considerable surface contamination at times. With low pressures and the use of the rubber tip a small amount of solution may be forced back into the instrument. There was no contamination of the fingers of the operator. In practice the tip is cleansed with alcohol after an injection is given. After several

injections with the use of the rubber tip and low pressure, the inside of the apparatus must be cleansed. This factor of contamination is obviously important in the use of radioactive materials.

The next phase of the investigative studies was one which has been considered also by many other investigators, namely, the relationship of the injection stream to vascular channels. There is some superficial bleeding attendant upon the use of the hypospray.® With the rubber-tip applicator the bleeding is often reduced in amount and may be delayed. Observation of the cutaneous surface at magnifications of 40 to 100 times at varying intervals after injection has enabled us to study the pattern of the skin puncture and the attendant bleeding, if any. Previous investigators with long series of clinical experience with the instrument have reported no intravenous injections.[3] From experiments on dogs, Brown [4] indicates that the "possibility of unintentionally penetrating a major vein with the jet is small, but the risk is always present." These experiments have not been repeated with the use of low pressure with the rubber-tip applicator. Hingson [5] adds, "We do not believe that the possibility of an inadvertent intravenous injection is as likely as with the needle and syringe method." In our clinical series, we have had one moderate hemorrhage from the injection site in a perianal area, one hemorhage from the tip of a finger with the use of procaine hydrochloride for the anesthetizing of a wart, one extensive hematoma on the dorsum of the hand in an elderly person, one hematoma over the bridge of the nose, and one superficial dissecting hemorrhage in a plaque of lichen sclerosus et atrophicus. It is our practice in areas where bleeding may be encountered to use a small cotton sponge with pressure over the injection site as soon as the hypospray® is removed. In fixed-tissue preparations with trypan-blue sections, no involvement of moderate-sized vessels could be observed. However, clinical observations have shown that sometimes there may be rupture at least of the superficial blood vessels by the injection stream. Clinical experiments are continuing on such sites as the scalp, forehead, hand, and lower legs to determine the factors underlying damage to vessels. The repeated injections of oil suspensions of penicillin in a series of syphilitic patients, now under study, revealed no evidence

3. Figge, F. H. J.: Injections Without Needles, Am. Pract. **1**:465, 1947. Figge, F. H. J., and Barnett, D. J.: Anatomic Evaluation of a Jet Injection Instrument Designed to Minimize Pain and Inconvenience of Parenteral Therapy, Am. Pract. **3**:197-206, 1948. Hingson, R.; Easley, E. J.; Gray, A. L.; Tucher, C.; Kiesselbach, M. R.; Parkhurst, G.; Usher, G., and Davidson, H.: Hypospray Administration of Penicillin in the Treatment of Gonorrhea, J. Ven. Dis. Inform. **29**:61-62, 1948. Hughes, J. F.; Jordan, R. G., and Hill, F. S.: Jet Injection in Pediatric Practice, Memphis M. J. **23**:116-120, 1948. Hingson, R. A., and Hughes, J. F.: Clinical Studies with Jet Injection: A New Method of Drug Administration, Anesth. & Analg. **26**:221-230, 1947. Tuohy, E. B.: Personal communication to the authors. Hirsch, H. L.; Welch, H.; Milloff, B., and Katz, S.: Administration of Penicillin and Streptomycin by Means of the Hypospray Apparatus (Jet Injection): Absorption, Toxicity, and Stability, J. Lab. & Clin. Med. **33**:805-810, 1948. Hingson, R. A., and others: Preliminary Study of the Hypospray for Parenteral Therapy in Its Relation to the Management of Leprosy, Internat. J. Leprosy **16**:173-178, 1948. Hughes, J. G.; Jordan, R. G., and Hill, F. S.: Current Status of Jet Injection, South. M. J. **42**:296-302, 1949.

4. Brown, R. V.: Evaluation of Certain Dangers in the Use of Jet Injection Technic, Proc. Soc. Exper. Biol. & Med. **70**:507-509, 1949.

5. Hingson, R. A.: The Development of the Hypospray for Parenteral Therapy by Jet Injection, Anaesthesia **10**:66-75, 1949.

clinically of intravascular injections. So it appears in most instances, especially with regard to the superficial vessels, that the stream at tremendous velocity will go right through the thin wall of the vessel and may even lacerate the wall. We agree with previous investigators, then, that jet-injections "should not be made in the neighborhood of large [blood] vessels unless the drug to be injected is safe [both in concentration and pharmacologically] for intravenous injection." [4] In clinical practice, when intravenous injections are to be given, the hypospray® cannot be used.

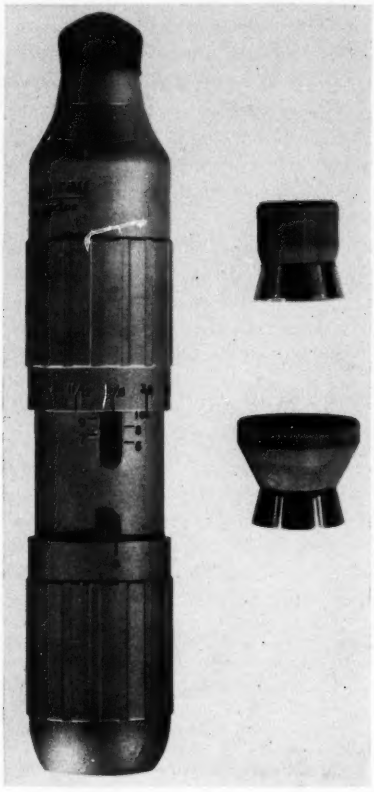

Fig. 1.—Hypospray® jet-injection apparatus. The black tip is for deep injection, and the rubber tips, for superficial injections.

Additional investigations on human and animal skin are concerned with the penetration of the appendages of the skin, with special reference to the hair follicle. It occurred to one of us (R. G. T.) that this instrument could be utilized in the treatment of fungus infections of the hair. Tracer studies with trypan blue showed that the dye could be found on the cuticle and in the cortex of the hair shaft and, in some instances, in the intrafollicular portion. The injection of various types of fatty acids is being investigated now in the skin of animals.

In the actual clinical use of the hypospray® it is desirable to have the surface of the skin dry so that the tip of the apparatus will not slip on injection. A linear or jagged laceration instead of a single small puncture may result if slipping occurs. This point is more important, perhaps, with regard to deeper injections, when the pointed plastic tip is preferred. Ordinarily, the surface of the skin and the tip of the instrument are cleansed with 70% alcohol or another type of cleansing material and allowed to dry. If there has been extensive contamination of the instrument with previous injections, the instrument must be cleansed thoroughly. Before the first injection is given, it is well to explain that the instrument will make a loud "popping" noise. The patient must not become alarmed, for sudden movement may cause the

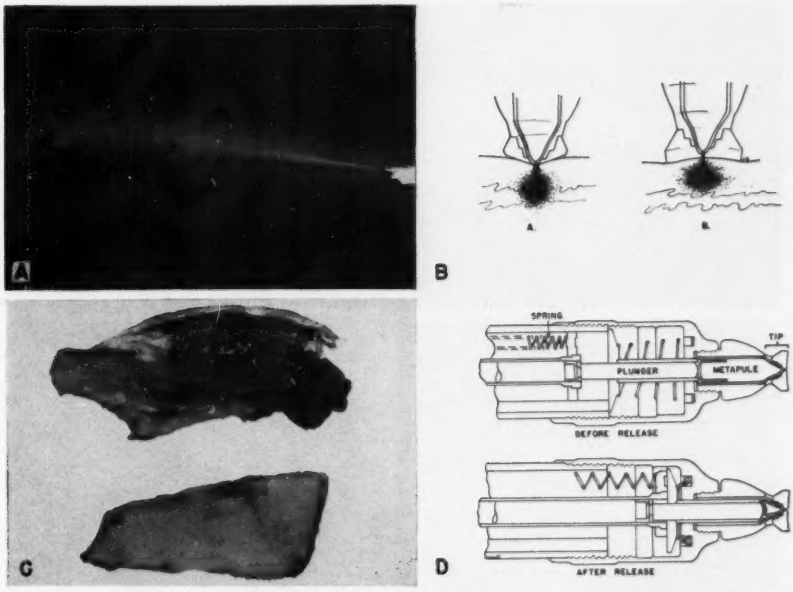

Fig. 2.—Some types of jet injection from the hypospray.® *A*, spray from the instrument against a black background showing the pathway of the fluid (black-and-white print from kodachrome®). *B*, schematic representation of (*A*) plastic tip and (*B*) rubber tip, showing how the plastic tip pushes the skin down, resulting in deep infiltration, and the rubber tip forces the skin up, with resulting superficial infiltration. *C*, postmortem tissue showing actual depth of penetration with the plastic tip (pressure *1A*) (upper) and the rubber tip (pressure *3A*) (lower); trypan blue dye used as tracer substance. *D*, cross section of the hypospray® instrument before and after ejection.

tip of the apparatus to slip. The apparatus must be held firmly against the skin. If one is concerned about the patient's moving, a wad of cotton may be held all around the tip of the instrument. With the more superficial type of injection, there may be some slight transient pain and perhaps even burning, depending on the material used and the area injected. As indicated in previous reports, the pain is less than that produced by the hollow-needle technics.

The hypospray® lends itself admirably to the local use of anesthesia for removal of biopsy specimens from the skin. With the rubber applicator tip it has been possible to take biopsy specimens in areas where the hypospray® could not have been used previously. These areas include the finger, the lobe of the ear, the tip of the nose, and the scalp. With a covering over the handle after insertion of the metapule® and setting of the correct pressure reading, the hypospray® may be used in sterile operating-room technics.

Two per cent procaine hydrochloride [5a] has been used in the ordinary biopsy technic. The hypospray® is put adjacent to the area of the lesion so that infiltration spreads diffusely into the lesion. On the finger, nose, ear, scalp, forehead, and cheek,

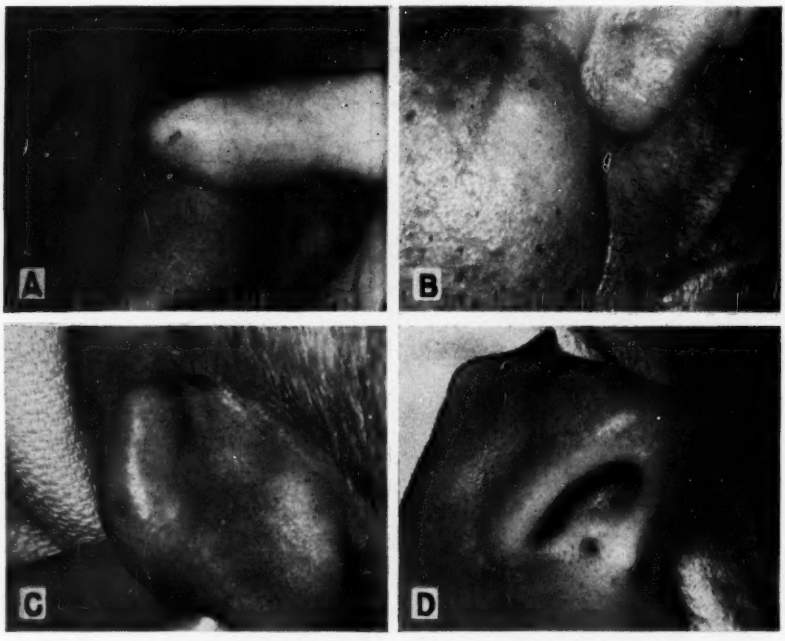

Fig. 3.—Local infiltration anesthesia by hypospray® injection. (Black-and-white prints from kodachrome.®) *A*, tip of the finger; pressure *3A* with rubber tip, *2%* procaine hydrochloride. *B*, cheek; pressure *3A* with rubber tip, *2%* procaine. *C*, lobe of ear; pressure *3A* with rubber tip, *2%* procaine. *D*, nose; pressure *3A* with rubber tip, *2%* procaine.

the pressures of *3A* to *3C* may be used. For areas that show deeper involvement, correspondingly greater pressures are used. Ordinarily, the content of one metapule,® approximately 1.0 cc., is adequate for removal of small biopsy specimens. For excision of larger areas, more injections may be given. When anesthesia is not complete, a second injection may be given directly over the original site. With the use of procaine, the hypospray® has been employed in minor surgical procedures,

5a. The procaine hydrochloride used in this study was "hypofil" procaine obtained from Dr. Geoffrey W. Rake, E. R. Squibb & Sons, New York.

both with the scalpel and with the electrosurgical technic. Investigations are now under way on its use in biopsy specimen removal and surgical treatments of the mucous membranes.

Considerable data have been collected to determine the effect of tissue distortion by the hypospray® injection. At the point of injection there is a small laceration of the skin. An irregular, often sharply demarcated area of tissue distortion of mild degree occurs in the immediate path of the fluid, but adjacent to this area there is no tissue destruction.

In dermatopathological conferences repeated efforts were made to determine whether the particular skin biopsy specimen under discussion was infiltrated by a needle or with the hypospray.® It was impossible for one to differentiate the two technics without examining the immediate area. Biopsies done on very fragile lesions have shown no distortion of architecture in connection with the use of the hypospray.® We believe, then, that with the hypospray® apparatus and the cutaneous punch the dermatologist has today a very simple and rapid technic for the performance of skin biopsy.

One of the earliest studies with the hypospray® in our department was of the local treatment of so-called neurodermatitis. This was investigated because of our interest in the psychodynamics of neurodermatitic reactions. Previously, procaine administered by the hollow needle had been used as one of the more-favored technics in the attempt to relieve itching in these thickened, uncomfortable patches. We preferred injections of procaine over those of alcohol. With the hypospray,® a much more efficient and effective technic was available. Two per cent procaine hydrochloride was used. The pressure varied according to the thickness of the lesion and whether we injected the procaine around the lesion or directly into it. In preliminary studies on 37 cases it was found that intralesional injection was superior to perilesional injection. Pressures between *2A* and *3A* were employed. The first treatment was usually a single injection to accustom the patient to the instrument. Every four to five days additional injections were given. Approximately one injection per 16 sq. cm. of area of lichenification has been found adequate. There have been no local or systemic reactions to therapy except in one patient, who complained of weakness and tachycardia after infiltration of a deep patch above the elbow. To rule out psychogenic reaction, a saline solution was given at the next injection. The local pain was so severe that no more treatment with the hypospray® was given. As a control technic in another case, the hypospray® was used without a metapule® in the apparatus. This method is injurious to the apparatus, and so it was not repeated. With the special applicator tip, pressures of *3B* and *3C* have been used on neurodermatitis of the scrotum. The response in neurodermatitis, then, varied according to the duration of the lesion, the thickness of the lesion, and, of course, the underlying psychodynamics. At the time of writing, in the series of 37 cases, 18 cases had been observed for three to four weeks; of these, 13 showed improvement and five were unimproved. In none was the condition aggravated. No additional topical therapy was needed in the 13 patients. Nineteen cases were still under observation, with subjective improvement but no change in the appearance of the lesions. Perhaps injections at more frequent intervals would have produced better results. To avoid confusion in this series, patients receiving surface phenolization after procaine injection were not considered for the time being. It is our clinical impression that repeated jet-injections of procaine with the hypospray® constitute an effective local

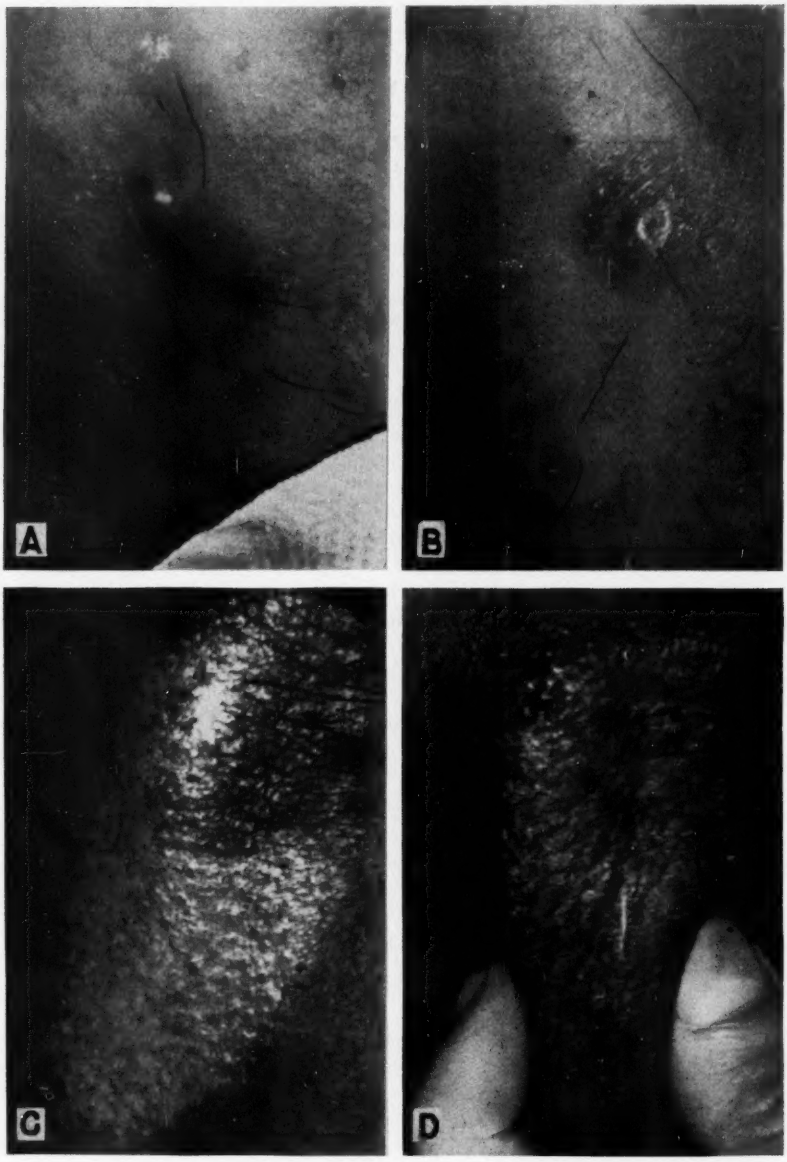

Fig. 4.—Therapeutic effects. (Black-and-white prints from kodachrome.®) *A*, furuncle before therapy. *B*, furuncle two days after single injection of 300,000 units of aqueous procaine penicillin, (crysticillin® suspension). *C*, neurodermatitis of the elbow before therapy. *D*, neurodermatitis two months after procaine treatment with the hypospray®; complete subjective response.

treatment for neurodermatitis. As a rule, the treatment ought to be continued for at least one month, since improvement does not begin until after that period.

In three cases of atopic dermatitis, hypospray® injections of *2%* procaine hydrochloride were given into single areas. An attempt was made to determine whether there was any selective relief of pruritus in these areas. The results were compared with the condition in control areas of equal intensity on similar areas of the body. In none of the three cases were there any significant subjective or objective changes after a series of one to four injections.

A series of three cases of dermatitis artefacta was used to determine whether the type of apparatus and method of injection would influence the patient from a suggestive aspect. In these cases procaine was injected in small areas. There was no improvement. In one case there was considerable aggravation of the condition because the patient felt certain that "poison" had been injected into her system. The response in all these cases was much less than with localized neurodermatitis.

Eight cases of pruritus vulvae were treated. In each case there was a single, so-called trigger point of pruritus of unknown etiology. In only one of the cases immediate symptomatic relief was afforded by hypospray® injections with *3A* to *3C* pressure of *2%* procaine hydrochloride. Some patients received five injections. There was slight laceration of the mucous membrane. Eight cases of pruritus ani without lichenification were also treated. There was no improvement. However, in five cases only *2%* procaine was used and no extensive infiltration was done. In one case complete relief following the injection of procaine into two "trigger-points" lasted for four to five days.

A miscellaneous group of patients with pruritus was also treated. The group included persons with chronic diaper dermatitis, prurigo mitis, and insect bites. In this group the number of patients treated has been too small for us to draw any conclusions. Likewise, procaine has been used in herpes zoster for the attempted relief of pain. It is not possible to decide, as yet, whether the jet injection was of any value.

Antibiotic therapy with the hypospray® has been chiefly with penicillin. The first type of penicillin available for our use was procaine penicillin in *2%* aluminum monostearate. Each metapule® contained 300,000 units of penicillin. To test the efficiency of the drug given by this means it was used first for pyodermic infections. Thirty cases, including ones of acne induratum, ecthyma, folliculitis, impetigo, furuncles, carbuncles, and perifolliculitis capitis abscedens et suffodiens, were treated. Control studies were done by treatment of similar cases with penicillin injected by hollow needle. The average dosage was 300,000 units per day for six to seven days. All medication was given in the buttock as systemic therapy. The healing time did not differ in control studies. Two patients complained of more pain as compared with that in needle therapy. In four cases there was hard-nodule formation, which persisted for some time, at the site of injection. In one case a hematoma developed over the injected area and remained for several days; however, the patient had no complaints at the time of treatment. With ecthyma and impetigo, the results were uniformly good; in the deep infections, the results were either fair or poor. The chief advantage of the hypospray® technic, aside from convenience and decreased pain, was seen with small children, as the medication could be given without there being fear of a "needle."

After the initial trial with systemic therapy, actual local injection was investigated with the oil suspension. Twenty cases of pyodermic infection, such as cellulitis, furuncle, carbuncle, paronychia, acne conglobata, and folliculitis, were first treated. The control study was similar to that in the above investigation. Results varied in these cases. It appeared that the additional therapy, which consisted in the application of wet dressings, had as much to do with the improvement as did the penicillin. Two cases showing nodule formation from the oil suspension had gradual subsidence of that condition. In three cases of acne conglobata, the penicillin was injected directly over the infected area. Two days later, in each patient a large abscess developed, indicating a spread of the inflammation beyond the confines of the nodulocystic lesion, presumably from the force of the injection. Four cases of dermatitis papillaris capillitii were treated. Penicillin was injected into the involved area and the injection repeated at weekly intervals. In two of the cases the lesion subsided markedly, leaving only noninfected scarred areas. One patient has been resistant to therapy, and one case has been under treatment only recently but with an excellent initial response. With the use of the new applicator tips and aqueous suspension of penicillin, which we obtained only recently, it is felt that more definite results can be observed with local-infiltration technics. The aqueous suspensions are more comfortable, produce no nodules in the tissue, and allow local treatment of such areas as face, fingers, and toes. In several cases of superficial injections there appeared to be some increased local bleeding. Streptomycin was used in only one case, a resistant folliculitis decalvans. An injection of 1,000,000 units was given every three days for 10 days. There was marked improvement but no cure. The jet injection of bacitracin by hypospray® is under study. One patient with erysipelas has been treated. There was only slight burning on injection in this patient. One patient with recurrent herpes simplex of the finger has had locally administered procaine in an attempt to prevent recurrence. So far, he has had no additional episodes.

Procaine-penicillin suspensions given by hypospray® have also been used in the treatment of 51 cases of infectious syphilis. The results so far have been gratifying. There has been a steady decrease in the titer of the serologic reaction in all cases. Results of dark-field examinations have become negative within 18 hr. The complete report of these cases will be presented later after suitable follow-up studies. (Investigative studies have been suggested for local penicillin therapy of gonorrhea in the female.)

Two cases of persistent larva migrans were treated successfully by hypospray® in Cincinnati, one with stibophen (fuadin®) and one with procaine. Additional studies were conducted in collaboration with Wilson and Farrington [6] at Jacksonville, Fla. The study was not a conclusive one because inadequate supplies did not allow complete treatment schedules to be followed. A third patient received jet injections of diethylcarbamazine (hetrazan®), stibophen, procaine, and saline solution with no results. Larva migrans and other parasitic diseases should be investigated critically with hypospray® technics.

The use of the hypospray® has been studied with interest in a number of miscellaneous conditions. In a series of six cases of granuloma annulare, procaine was injected directly into the individual border of the lesion. It was thought that the

6. Wilson, F., and Farrington, J.: Personal communication to the authors.

hypospray® treatment did help. In no case was there any dramatic or immediate clearing. The only control was the duration of the lesion before hypospray® treatment. There was no control series with saline solution or other types of materials or with cases having spontaneous involution. Compared with other forms of topical therapy, including the hollow-needle infiltration of the active lesion of granuloma annulare, it was felt that in this small series the hypospray® was effective. In three cases of erythema perstans, selected areas were treated with procaine, since the patients were sensitive to penicillin. Transient improvement occurred in the local injected area in only one patient. Three cases of lichen sclerosus et atrophicus were studied from an investigative aspect, chiefly as regards bullae formation and production of small intradermal hemorrhage. The lesions were very extensive and represented various phases of development.

Another interesting series was encountered in the investigative studies of the hypospray® injection in necrobiosis lipoidica. Four cases of this disorder were studied. Two occurred in diabetics; two, in proved nondiabetics. An attempt was made to control the study by the identification of lesions as early or late, by the treatment of only small areas of an actual plaque, and, finally, by the separate use of procaine, insulin, and hyaluronidase on separate areas. In spite of the pathology of necrobiosis, a hypercholesteremic disease with vascular changes, it was felt that, since this condition is refractory to treatment, a study of local therapy would be warranted. From our initial experiments in this small group, it seemed as though insulin had a greater value than procaine or hyaluronidase. The experiments will be reported in detail at a later date. Lobitz [7] has reported recently a spontaneous cure of necrobiosis lipoidica. Since this report was submitted a detailed study has been made of cortisone by hypospray® injection.

These preliminary observations over a period of two years show only a few of the many studies which could be done in dermatology with the jet-injection apparatus. The whole field of enzymes and the possibility of injection therapy of accessible malignant growths will provide two main studies for the future. It is certain that many more applications will be found for the use of this apparatus.

The reactions to the jet injections have not been too frequent or too significant in our hands. The hemorrhages have been mentioned before. The other reactions have been in persons suspected of procaine sensitivity—one patient with tachycardia, anxiety and weakness, mentioned above, and two patients with a "chemical type" of retrograde-lymphangitis-like condition developing after an injection with 2% procaine. This reaction consisted in the immediate appearance of a streak from the injection site, in one instance, from the neck up into the scalp, and in the other, from the middle third of the extensor surface of the forearm down to the wrist. The reddened streak lasted for several hours and in one patient was associated with a broad band of anesthesia. Subsequent skin tests elicited negative reaction to procaine. No eczematoid dermatitis has been produced as yet with such highly sensitizing materials as penicillin. The problem of contamination of the apparatus has been mentioned previously. No secondary infections have been observed in any of the patients of our series. The metapules® receive the same bacteriologic controls as do mixtures in glass ampules.

7. Lobitz, W. C.: Personal communication to the authors.

The apparatus is, of course, a precision instrument and will probably be expensive. One must learn how to use it. The noise is still a disturbing feature for the patient receiving his first injection. Some materials may not be stable in the metapule.® Additional investigative studies are needed to work out the biophysical applications of jet-pressure injections in the skin.

CONCLUSIONS

The hypospray® is a spring-activated high-pressure injection apparatus offered as a substitute, under certain conditions, for the hollow needle now used. The dermatologic aspects of the hypospray® have been studied for more than two years. With various types of tracer techniques, efforts were made to study the pathways and depth of penetration. Studies have been made of various types of applicator tips as related to the use of this instrument on normal and pathological skin.

Therapeutic studies have been carried out chiefly with regard to the production of local anesthesia in biopsy technics and the therapy of localized neurodermatitis, local inflammatory and parasitic disorders, and other miscellaneous conditions. The limitations of the instrument have been listed. The hypospray® apparatus appears to be of value in dermatology.

ABSTRACT OF DISCUSSION

Dr. Joseph M. Hitch, Raleigh, N. C.: It is indeed a pleasure to discuss this presentation by Dr. Preston and his associates, though I fear I have little to add. The manufacturers of the instrument have been kind enough to supply me with a hypospray® and metapules® of several medicaments. However, this equipment has been available to me for only the past two months; therefore, my experience is distinctly limited.

The advantages and limitations of the apparatus have been presented in a very conservative fashion. That jet injections are generally much less painful than those with the usual needle-and-syringe apparatus is unquestioned. This aspect is an important consideration in general. Obviously, it is an especially important factor in mass immunizations, pediatrics, insulin administration, and similar fields. It would seem to me, though, that the method should have more advantages than painlessness to justify its special consideration in dermatology.

In comparing the two technics of percutaneous medication in the field of dermatologic therapy one cannot escape the very attractive thought that if the jet injector could be adjusted so that the medication would be spread over a larger field within the dermis or superficial subcutaneous tissues, a wide range of usefulness in dermatology would be opened. I believe that the soft rubber nosepiece, which I understand was designed by Dr. Goldman, is a definite improvement in this respect. When it is used with low spring pressures it has seemed to me that immediate diffusion in the superficial tissues is rather good. Perhaps further mechanical refinements will make the apparatus even better.

Along this same line, the work presented here and that still under investigation at the University of Cincinnati on the treatment of various forms of mycotic and bacterial folliculitis offers great promise for improved therapy in many recalcitrant conditions. The authors' studies relative to the tissue distribution of dyes and other tracer substances and those pertaining to sodium fluorescein and surface contamination should certainly be continued as changes in the apparatus may be made from time to time.

The usefulness of the hypospray® in cutaneous biopsy is, I think, somewhat limited, since it is questionable whether several jet injections at the same site represent a procedure which is more desirable than a single injection with a small-gauge needle. However, I do agree that, barring hemorrhage, the tissue is no more distorted with jet injection than with the needle technic, and therefore use of the hypospray® is just as satisfactory for microscopic examination.

Circumscribed neurodermatitis certainly appears to be a cutaneous condition which would lend itself admirably to treatment by jet injection. My experience with treating this condition

with subdermal injections of procaine by this method has been similar to that reported by Dr. Preston and his associates. I have had one experience with circumscribed neurodermatitis which I should like to mention in order that others might enlarge on the possibilities. This experience concerns a patient who had a severe neurodermite over the coccygeal area which had been treated for a long period with various remedies, all without striking success. When the hypospray® became available, I started him on treatment with jet injections with 2% procaine hydrochloride. He seemed to improve slightly but, after about six or eight such injections, had a partial relapse. In the meantime, I had had prepared metapules® containing diphenhydramine (benadryl®) hydrochloride, 10 mg. per cubic centimeter. Without telling the patient that any change had been made in medication, I employed it by jet injection, using the same technic as with procaine. At the next visit, after the first diphenhydramine injections, he volunteered the information that he was distinctly better. On inspection, the lesion was found to have decreased in size about a third, and a considerable amount of the scaliness was gone; with four more injections of diphenhydramine, the patient now appears almost well. He still maintains that this medication is infinitely superior to the procaine. Perhaps the authors will try this substitute for procaine in lichen simplex chronicus if they have not already done so.

I believe there is a possibility that jet-injection technic employing a sclerosing agent may be adaptable to the treatment of selected cases of hemangioma. The manufacturers of the hypospray® have prepared for me metapules® containing various dilutions of sodium psylliate (sylnasol,® Searle) and an additional set of plungers so that it is possible to deliver less than the 0.6 cc. minimum delivered by the present apparatus.

Currently, only animals have been given injections of this sclerosing agent, the sites of injection afterward being excised and studied microscopically for depth and breadth of inflammatory reaction and necrosis. I believe there is a definite possibility that this form of treatment will ultimately work out well for hemangioma.

I was interested in what Dr. Preston said in regard to the treatment of larva migrans by jet injection. Beginning about this time of year it is one of the plagues of the dermatologists in North Carolina. I am anticipating trying this method of therapy during the summer. This method of administering stibophen (fuadin®) or other larvacides seems to hold promise, but, again, difficulties may be encountered because of too much penetration and too limited spread of the medicament. Perhaps we can learn to overcome these difficulties with increased experience.

The hypospray® as now designed is certainly mechanically satisfactory. As far as this group is concerned its usefulness will depend on whether or not clinical and research dermatologic objectives can be accomplished with it which were impossible or less satisfactory with needle and syringe. I believe that such will be the case. The studies of Dr. Preston and his co-workers have demonstrated admirably a few definite indications for the use of this apparatus and have pointed out several other possible uses which these workers are continuing to investigate. Such work as this should ultimately lead to a real and valuable new tool in dermatologic therapy.

DR. ROBERT H. PRESTON: I want to thank Dr. Hitch for his discussion. In regard to biopsy technic, we have removed over 200 specimens at the Cincinnati General Hospital with the use of the hypospray® apparatus, and there was little or no damage to the tissue as observed under the microscope.

LICHEN SIMPLEX CHRONICUS AND ITS VARIANTS

A Discussion of Certain Psychodynamic Mechanisms and Clinical and Histopathologic Correlations

BERTRAM SHAFFER, M.D.
AND
HERMAN BEERMAN, M.D.
PHILADELPHIA

IN THIS presentation we will attempt to demonstrate from the clinical and histopathologic standpoint an association between a number of eruptions having in common the element of lichenification. This group includes lichen simplex chronicus and its variants, prurigo nodularis, lichenificatio gigantea, and certain phases of the Sulzberger-Garbe syndrome. We intend, furthermore, to point out that these processes are frequently related to some emotional disturbance. In addition, we shall emphasize that the diagnosis of such psychogenically induced dermatoses often can be made by the clinician on the basis of positive dermatologic and histopathologic findings, rather than by resorting to the negative criterion of exclusion.

Without going into a detailed psychiatric explanation, we shall elucidate some psychodynamic mechanisms that may give rise to these cutaneous changes.

Emotions are part of the basic hereditary equipment for adaptation. They represent the sensory component of visceral responses (mediated by way of the autonomic and endocrine systems) to the adaptive strains of life.[1]

When adaptation is adequate to meet the subjective needs of the individual, the emotional problem is readily and satisfactorily solved, and the organism, after a temporary period of emotional and visceral reaction, i. e., excitement or tension, rapidly regains a state of equilibrium, i. e., relaxation. Physiological aspects of this phenomenon have been described as homeostasis by Cannon[2] or as the general adaptation syndrome by Selye.[3]

Read in a symposium on Psychosomatic Medicine and Dermatology, at the American Academy of Dermatology and Syphilology, Chicago, Dec. 5, 1950.

From the Departments of Dermatology and Syphilology, University of Pennsylvania, School of Medicine, Dr. Donald M. Pillsbury, Director, and the Graduate School of Medicine, Dr. Herman Beerman, Chairman.

1. (*a*) Brunner, M. J.: Biologic Basis of Psychosomatic Disease of the Skin, Arch. Dermat. & Syph. **57**:374 (March) 1948. (*b*) Seitz, P. F. D.: An Experimental Approach to Psychocutaneous Problems, J. Invest. Dermat. **13**:199 (Oct.) 1949. (*c*) Miller, M. L.: Psychodynamic Mechanisms in a Case of Neurodermatitis, Psychosom. Med. **10**:309 (Nov.-Dec.) 1948. (*d*) Stokes, J. H., and Beerman, H.: Psychosomatic Correlations in Allergic Conditions: A Review of Problems and Literature, ibid. **2**:438 (Oct.) 1940. (*e*) Cormia, F. E.: Psychosomatic Factors in Dermatoses, Arch. Dermat. & Syph. **55**:601 (May) 1947.

2. Cannon, W. B.: The Wisdom of the Body, ed. 2, New York, W. W. Norton & Company, Inc., 1939.

3. Selye, H.: Textbook of Endocrinology, Montreal, Acta Endocrinologica, Inc., 1947, p. 837.

If, however, the organism fails to find a satisfying solution for its emotional problem, then the tension or the excitement engendered by the adaptive stimulus cannot be discharged in a subjectively effective fashion—i. e., relaxation is not possible—and so the accumulated emotional potential must be dissipated in an abnormal manner. This may take the form of peculiar and seemingly useless behavior (neuroticism), or it may become manifest as an organ reaction (a psychosomatic reaction). The actual emotion giving rise to this reaction may be so repressed because of its obnoxious content that the patient on superficial emotional investigation is completely unaware of its presence, or he may resist with great vehemence and indignation any attempt to bring this material into open acknowledgment.[1c]

The skin participates frequently as a substitute organ of expression for pent-up emotional tension,[4] and, as the recipient or sounding board of this nervous bombardment, it reacts with a wide variety of patterns. These include vascular dilatation or constriction, changes in vascular permeability, modification in glandular activity, sensory radiations, such as itching and paresthesias, and kinetic activities on the skin (rubbing, scratching, biting, and picking the skin and its appendages).[5]

These sensory aberrations and kinetic activities, particularly rubbing and scratching, are the manifestations with which we are chiefly concerned. Chronic scratching and rubbing trauma to the skin may be the result of psychogenically induced pruritus or paresthesias, or it may stem from a kinetic discharge of nervous tension with destructive effects on the skin. In either case it leads to excoriation, eczematization, or lichenification.

We believe that it is often possible to identify with some degree of precision emotionally induced rubbing and scratching of the skin with its traumatic sequelae, particularly when it leads to lichenification or one of its clinical variants. This may be done by an objective clinical and histopathologic examination of the skin itself and by observation of the patient's behavior with reference to his skin while under examination, coupled with a careful history with regard to the patient's cutaneous symptoms.

This does not imply that we regard the total examination of the patient, including all his organ systems and an appropriate psychiatric appraisal, as of little importance. On the contrary, we feel strongly that a general evaluation of the patient *in toto* cannot be recommended too strongly. What we do wish to emphasize, however, is that the skin itself tells its own story and that we, as dermatologists, can contribute in a positive manner to a diagnosis of an emotional disturbance, rather than depending on such a diagnosis by exclusion after ruling out various "organic" causes.

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4. Klauder, J. V.: Psychogenic Aspects of Skin Diseases, J. Nerv. & Ment. Dis. **84**:249 (Sept.) 1936. Wright, C. S.: Psychosomatic Factors in Dermatology, South M. J. **42**:951 (Nov.) 1949. English, O. S.: Role of Emotion in Disorders of the Skin, Arch. Dermat. & Syph. **60**:1063 (Dec.) 1949. Seitz, P. F. D.: Psychocutaneous Aspects of Persistent Pruritus and Excessive Excoriation, A. M. A. Arch. Dermat. & Syph., to be published.

5. Brunner.[1a] Stokes and Beerman.[1d] Cannon.[2] Michelson, H. E.: Psychosomatic Studies in Dermatology, Arch. Dermat. & Syph. **51**:245 (April) 1945. Seitz, P. F. D.: Psychogenic Conditioning During the First 2 Weeks of Life, Psychosom. Med. **12**:187 (May-June) 1950. Rothman, S.: The Role of the Autonomic Nervous System in Cutaneous Disorders, Psychosom. Med. **7**:90 (March) 1945. Seitz.[1b]

The following are some of the characteristics by which emotionally related rub-and-scratch trauma to the skin may be identified.

1. The patient often complains of pruritus out of all proportion to the extent of the presenting dermatitis. The bitterness with which many of these patients complain, the excruciating agonies, and the loss of sleep and exhaustion that result are very striking when one views the minimal cutaneous signs that they are apt to display. This exaggeration of the subjective findings over the objective evidences is common, of course, not only in skin but in many psychogenically induced organ relationships.

2. The itch is apt to develop at certain characteristic times for each individual patient. This may be in one of the following situations: (*a*) in the evening after returning home at the end of the day's work or after eating the evening meal; (*b*) when the patient thinks about going to bed or when the patient disrobes for bed (in women especially with removal of the corset or girdle); (*c*) when the patient is just about to doze off to sleep; (*d*) when the patient falls asleep readily enough but awakens scratching violently within an hour or two or in the early morning hours (5 to 6 a. m.), after which further sleep is often impossible because of the severe pruritus.

The explanation for these time incidences may be that during the day, because the patient is preoccupied with his usual business activities and diversions, the emotional symptom is repressed. At the end of the day, when he attempts to relax, the accumulated emotional potential, not having been effectively dissipated, interferes with rest and sleep in the form of violent pruritus and scratching.

3. A trigger zone is often present, i. e., a certain highly localized spot in the involved region, if lightly touched or brushed, sets off a rapidly spreading crescendo of pruritic violence.

4. The orgiastic nature of the itching is often remarkable. The severe and maddening pruritus and, consequently, the scratching and rubbing, mount with increasing fury to cease only with a climactic exhaustion of the patient and severe damage to the skin.

5. The itch develops in crises and paroxysms. In between, for many hours at a time, the patient may be completely free of pruritus, although he may complain of pain and soreness as a result of the trauma inflicted on the skin.

6. In contrast to the above, in some cases there may be a complete and vigorous denial of pruritus and scratching, in spite of obvious extensive objective signs of rub-and-scratch trauma. The traumatic episodes very often occur at night while the patient is asleep and are, as a consequence, completely unknown to him in his awakened state. Substantiation of this scratch trauma is often given by the patient's spouse, who complains of loss of sleep due to the rubbing and grating sound of the patient's scratching. In the absence of this evidence, painting of the affected regions with some dye, such as methylrosaniline chloride (gentian violet) or Castellani's paint will usually result in staining of the scratching parts, such as the finger-tips or the opposite heel, and thus prove to the patient his subconscious behavior.

7. When consulting the physician, the patient subconsciously but characteristically rubs and scratches his skin when discussing his symptoms or troubles. He may be doing this even while he denies with finality any participation in this type of activity, thus indicating its profound subconscious nature.

8. Certain favorite scratch sites are often utilized. These are usually in readily accessible areas and include the nape, the eyelids, the ankles, the lower third of the leg, the pubic region, the perineum and the anogenital region, the upper inner thigh region, and the ears. No region, however, is immune.

9. Secondary or associated scratch sites can often be determined, either existing concurrently or having been present in the past. When scratching in one site is "cured," it is apt to make its appearance at some future time elsewhere if the basic emotional disturbance remains unchanged.

10. Other evidences of the utilization of a kinetic discharge mechanism for emotional release can sometimes be observed. These include finger-nails polished from constant rubbing, evidences of biting the nails, and a history of sucking the thumb, pulling the hair, enuresis or some behavior disorder in childhood.

11. Covering the lesion, if this is practicable, with a firm occlusion dressing, such as Unna's paste boot, will often cause the lesion to improve and even disappear after several weeks, provided further that a scratching instrument introduced between the dressing and the skin has not been used surreptitiously. This method cannot be utilized if the skin is eczematized or greatly excoriated because of the danger of secondary infection.

12. The patient's emotional problem may be correlated with his symptoms as developed anamnestically. This sometimes involves profound psychiatric investigation, but often sympathetic and patient questioning will elicit a great deal of enlightening relevant information.

13. Psychiatric probing toward the core of the patient's emotional problem often gives rise to an acute exacerbation of the cutaneous symptoms, especially if the problem is one that has been strongly repressed and one that contains much emotional matter of objectionable content to the patient.

14. There may be a history of some incidental skin disturbance acting as a localizing and precipitating factor during a period of emotional disturbance. This may include contact dermatitis, pediculosis, seborrheic dermatitis, psoriasis, or acne vulgaris.

The cutaneous syndromes, associated with the 14 characteristics listed above, with which we are dealing are lichen simplex chronicus and its variants, prurigo nodularis, lichenificatio gigantea, and certain phases of the Sulzberger-Garbe syndrome. These processes, in our opinion, are not separate diseases but several stages or developments of a single pathologic disturbance characterized by variable expressions of lichenification. While the lesions may differ widely in morphologic and histopathologic details, certain common basic themes can often be discerned. Many transitional stages between the various members of this group are observed, and it is not unusual to find transmutation from time to time of one type of lesion into another or the appearance simultaneously of different lesions of this group in the same patient. Although Rothman has been unable to confirm this experimentally, it is our thesis that these variations are merely quantitative and/or qualitative modifications in the reactivity of the skin to persistent and repeated rubbing and scratching. The latter, in most cases, is due to an emotional disturbance.

LICHEN SIMPLEX CHRONICUS

In terms of the taxonomist, lichen simplex chronicus is the type species of this genus, inasmuch as it represents the simplest and commonest manifestation of the group and the one in which rubbing and scratching of the skin are generally accepted as etiologic factors. Synonyms for this entity include neurodermatitis circumscripta (Brocq), suboccipital dermatitis (Lynch),[6] certain types of pruritus ani, et scroti, et vulvae, and some forms of stasis dermatitis.

This eruption usually consists of a patch of lichenified skin that may be sharply demarcated but more frequently merges imperceptibly into the normal surrounding skin. This lichenification is indicated by thickening and accentuation of the normal markings of the skin. The furrows become deeper, and the intervening mosaic becomes elevated, shiny, and often covered with dull, grayish, adherent scales. As one approaches the periphery of the patch, these developments rather suddenly become less pronounced, and numerous discrete and confluent lesions are dispersed as satellites about the mother patch. One of the outstanding features of this dermatitis is the relative absence of erythema in proportion to the other skin changes.

In lichen simplex chronicus we subscribe largely to the histopathologic description presented by Sachs, Miller, and Gray [7] as the "neurodermatitic reaction." This reaction involves both the cutis and the epidermis (Fig. 1). The latter is usually acanthotic and shows some degree of regularity; there is, as a rule, little evidence of edema. A focal infiltration composed of small round and wandering connective-tissue cells is found about the vessels of the middle and upper layer of the cutis, and the walls of the arterioles and small arteries are thickened. These findings are not constant in all cases. In addition to the usual factors, "friction, scratching, medication, etc., may superimpose a traumatic dermatitis. This would account for the presence of an irregular acanthosis, edema, and even parakeratosis."[7] Sachs and his associates feel that these features are evidences of secondary eczematization.

There are some differences which have been described by other authors, and we believe they should be included in the histologic description. We refer especially to the matter of edema of the epidermis. We agree with Ormsby and Montgomery [8] that there are frequent areas of spongiosis, sometimes leading to a microscopic vesicle, but there are no microabscesses. Laymon,[9] on the other hand, believes that vesicles do not occur.

On the whole, therefore, while the histologic picture of lichen simplex chronicus is, generally speaking, nonspecific, strict attention to the various findings may make it possible for one to diagnose this process objectively in a large proportion of the cases.

The relatively characteristic clinical and histologic picture of lichen simplex chronicus may be modified by variations in the degree and kind of rubbing and scratching, by differences in the response of the skin to this type of stimulus, and

6. Lynch, F. W.: Suboccipital Dermatitis, Arch. Dermat. & Syph. **60**:307 (Sept.) 1949.

7. Sachs, W.; Miller, C. S., and Gray, M. B.: Neurodermatitic Reaction, Arch. Dermat. & Syph. **54**:397 (Oct.) 1946.

8. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948, p. 360.

9. Laymon, C. W., and Dixon, A. A.: Lesions of the Scalp in Certain Scaly Dermatoses: Histologic Study, Arch. Dermat. & Syph. **62**:181 (Aug.) 1950.

by the effect of certain local incidental elements. Description of some of these variations follows:

Excoriation.—The presence of punctate bloody crusts often in linear configurations obviously stems from scratching with a degree of trauma sufficient to remove the epidermis and to injure some of the superficial capillaries.

Changes in Pigmentation.—The development of leukoderma and hyperpigmentation modifies the clinical picture superficially, although the essential features of lichenification are still present. Both leukoderma and hyperpigmentation are com-

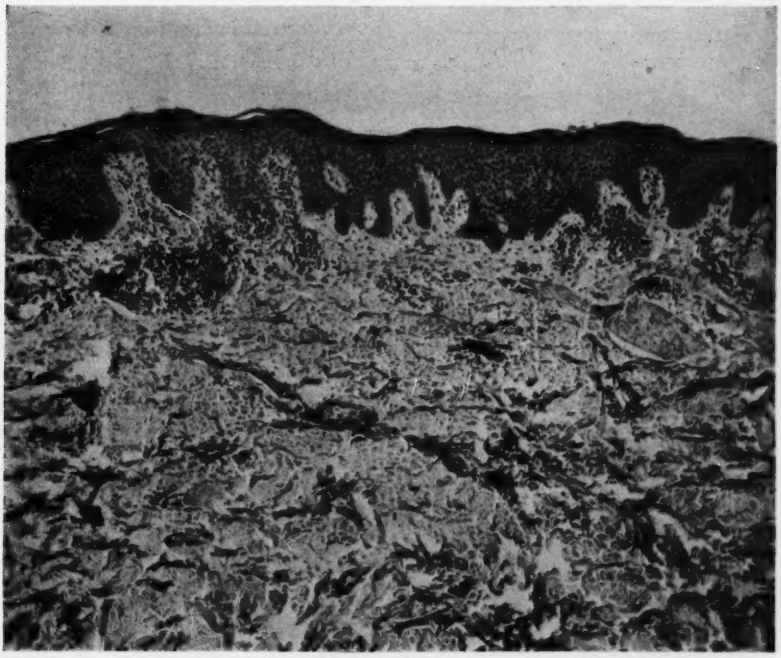

Fig. 1.—Section from an early case of lichen simplex chronicus illustrating the fairly regular acanthosis with minimal signs of edema. The scale is chiefly of a hyperkeratotic character. The basement layer is intact. The focal infiltrate is scanty and involves the upper and middle layers of the dermis.

mon manifestations of chronic dermatoses of many types and merely reflect the depression or stimulation of pigmentagenesis caused by the pathologic process.

Eczematization or Eczematous Changes.—When the epidermis is unusually thin, as, for instance, in infancy or in old age, or on certain parts of the body, such as the face, eyelids, sides of the neck, or on the intertriginous sites, eczematous changes are apt to occur because traumatization of the epidermis readily results in oozing, weeping, crusting, and edema, developing either concurrently or alternately with the lichenification. This may modify the basic features of lichenification in such a way as to render the diagnosis at times uncertain, although in most cases its specific features can at some time be identified. Contact dermatitis may be super-

imposed and produce secondary eczematous modifications of the basic process by too vigorous application of, or sensitization to, local medication or some other contactant. Secondary or associated infection with either fungi or bacteria, or the localization of the patch of lichen simplex chronicus at a site of previously active fungus or bacterial eruption, may also induce a clinical picture consisting of combinations of eczematous and lichenified lesions, sometimes with impetiginization.

Swelling.—Diffuse, deep-seated, persistent swelling of the affected region occasionally develops (Fig. 2). This is not the edema that occurs in the acute and eczematous phases of this disease, in which the patch becomes red, swollen, inflamed,

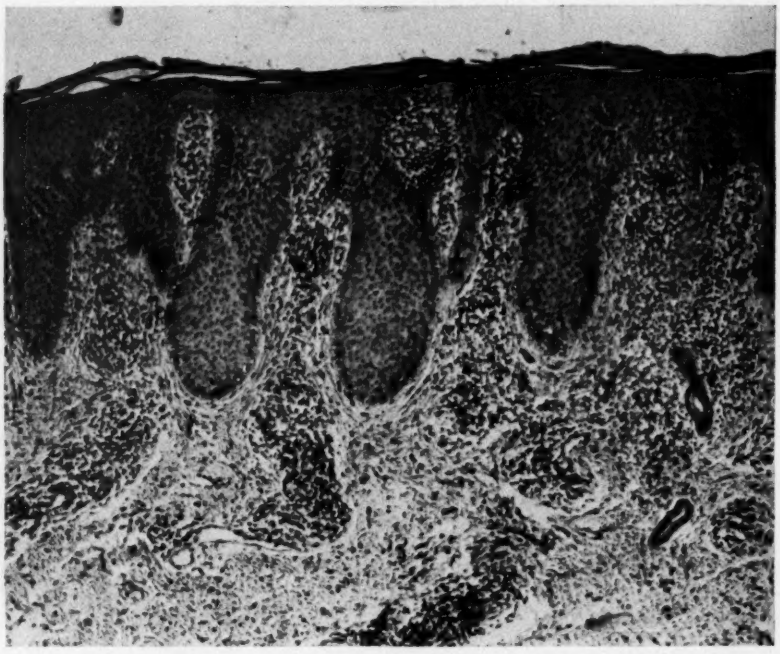

Fig. 2.—Photomicrograph from a lesion of lichen simplex chronicus manifested clinically as a deep, diffuse, nonpitting, smooth swelling of the affected part. Although the epidermis is acanthotic, the corium effects the major portion of the swelling as a result of dense, highly developed focal infiltrate and some diffuse fibrosis.

and weeping. The swelling described here is relatively noninflammatory, dense, nonpitting, and chronic. It appears as an essential part of the lichenified process and one in which the corium rather than the epidermis participates chiefly.

Follicular Eruptions.—The follicular types of lichen simplex chronicus is seen in hairy parts or in persons with unusually reactive follicular responses, i. e., Negroes. The individual lesions appear as discrete lichenified papules at the sites of the follicular openings, often pierced by a hair. Where the papules become confluent, they take on the picture, clinically and histopathologically, of ordinary lichen

simplex chronicus. If the follicular eruption is unusually widespread, it may resemble superficially lichen ruber moniliformis. This type of involvement is seen at times as one phase of the Sulzberger-Garbe syndrome.

Variations in Locale.—As might be expected, differences in the physiology and anatomy of the skin on various parts of the body are apt to produce different clinical responses to a given stimulus. On the occiput, for instance, and on the nape adjacent to the occiput the eruption is apt to take on a scaling character closely resembling seborrheic dermatitis, with which, indeed, it is often associated. Where the epidermis is unusually thin, eczematization rather than lichenification is apt to appear.

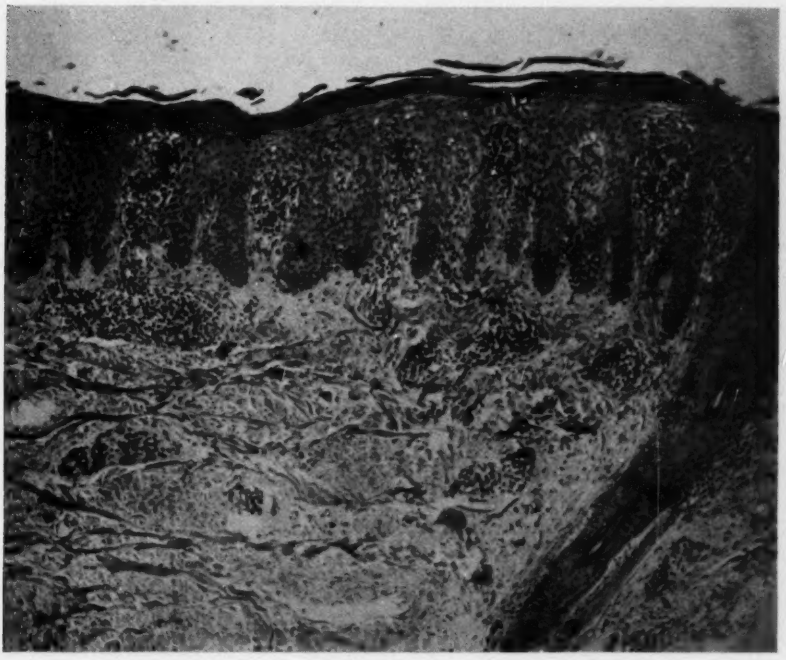

Fig. 3.—Photomicrograph from a patch of psoriasiform lichen simplex chronicus. This shows mixed characteristics of psoriasis and lichen simplex chronicus.

In intertriginous sites, in addition to the eczematization, the eruption is prone to become macerated, fissured, and secondarily infected with bacteria and fungi, and, because of the persistent heat, moisture, and friction, rugose hypertrophy of the epidermis occurs in the form of soft, soggy, macerated, thickened folds. This is the familiar picture of pruritus ani, pruritus perinei, and pruritus vulvae. When the palms and soles are the site of this process, the usual picture of lichenification is apt to be absent because of the great thickness of the stratum corneum. The affected site is usually a rather sharply demarcated plaque of thickened, scaly, and keratotic epidermis with almost no visible erythema. Deepening of the furrows and the shiny papules are not apt to be found. Here the diagnosis of dermatophytosis is fre-

quently made by the inexpert. The presence of stasis tends to produce, on the one hand, eczematous changes, and, on the other hand, it favors verrucoid hypertrophy and varying degrees of pigmentation and hemosiderosis. Many cases of so-called stasis dermatitis are in reality examples of masked lichen simplex chronicus.

Accompanying Dermatoses.—The role of incidental and accompanying dermatoses, such as psoriasis, lichen planus, seborrheic dermatitis, ichthyosis, and hyperhydrosis, in modifying the picture of lichenification is well-known. As one might anticipate, modifications often partake of the characteristics of both diseases (Figs. 3 and 4).

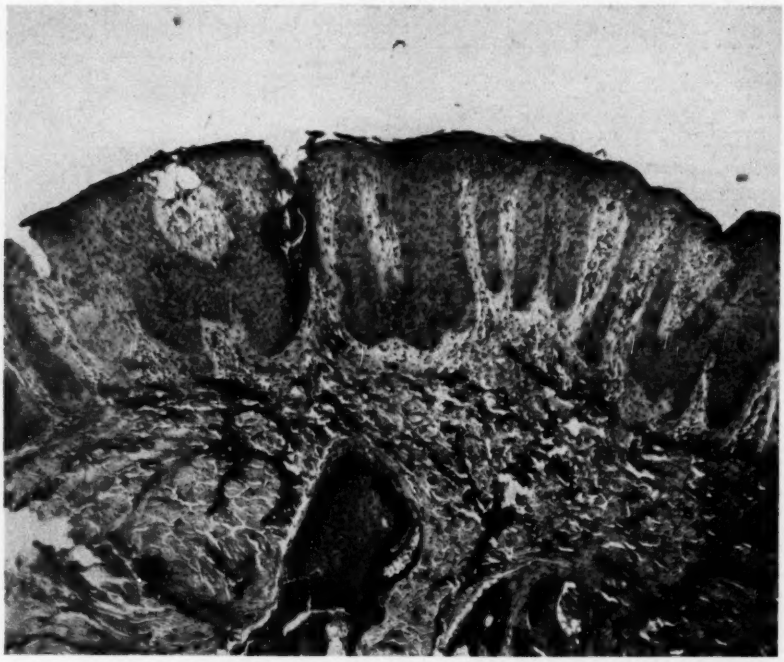

Fig. 4.—Section from a patient with lichen simplex chronicus superimposed on acne vulgaris. The features of lichen simplex chronicus are evident, associated with an inflammatory and fibrotic process about a deep-seated pilosebaceous organ (only partly shown here).

PRURIGO NODULARIS

The ultimate in hyperkeratotic development, so far as lichenification is concerned, is the discrete, hyperkeratotic, buttonlike eruption which occurs chiefly on the extremities and is called prurigo nodularis (lichen obtusus corneus; nodular lichenification [Pautrier]). In this eruption acanthotic and hyperkeratotic features are greatly accentuated and form the dominant part of the histologic picture (Fig. 5). In the corium there are vascular dilation, perivascular round-cell infiltration, and some connective-tissue proliferation. These changes seem to be due to the fact that the patient rubs and scratches intensely small discrete portions of the skin rather

than distributes the same degree of trauma over a large site as in lichen simplex chronicus. In certain patients all transitional stages, from eczematoid through lichenification to the typical lesion of prurigo nodularis, can be observed.

LICHENIFICATIO GIGANTEA [10]

The extreme expression of lichenification develops whenever verrucoid hypertrophy is favored, as in intertriginous or stasis areas. This has been called lichenificatio gigantea. As one might expect, it is found chiefly on the legs and in the intertriginous sites of the genitals and groins.

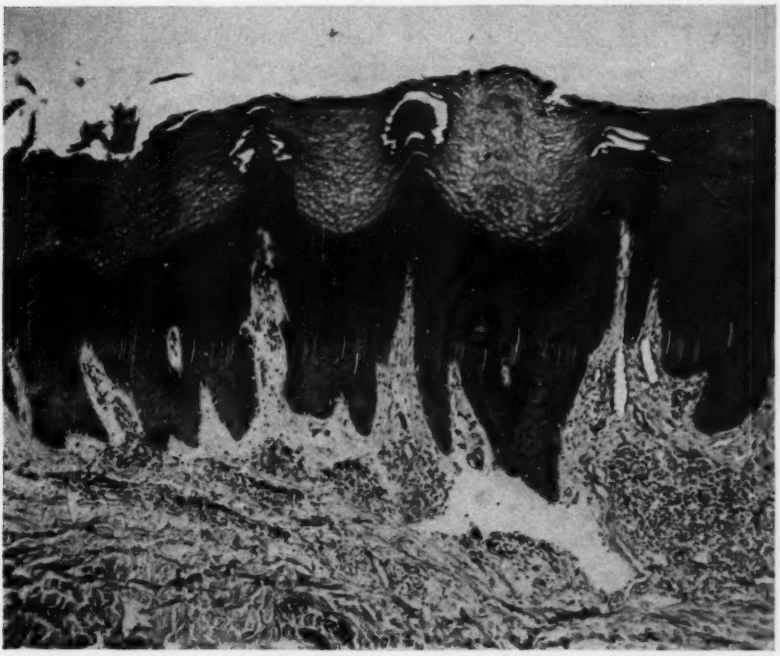

Fig. 5.—Histologic appearance of a lesion of prurigo nodularis. This demonstrates the dominant role that excessive hyperkeratosis and acanthosis plays in the production of the clinical picture.

Here the clinical picture is that of a strikingly developed verrucoid change in the skin in sharply demarcated patches. Almost no erythema is present. The hypertrophic formations may be elevated as much as 1 cm. above the surrounding surface. Usually at the periphery of the patch one can discern some evidence of ordinary lichenification, either as a diffuse involvement or as discrete, flat, shiny, angular lesions.

10. Berlin, C.: Lichenificatio Gigantea (Lichénification Géante of Brocq and Pautrier), Arch. Dermat. & Syph. **39**:1012 (June) 1939. Ronchese, F.: Neurodermatitis with Giant Lichenification, ibid. **43**:920 (May) 1941.

The histologic picture is that of extreme rugose and verrucoid hypertrophy of the epidermis with long penetrating epithelial pegs and deeply set furrows. There is a moderately developed hyperkeratosis. The papillary bodies are broadened and elongated and are the site of a rather intense round-cell infiltrate. In the middle portion of the corium, the infiltrate is focalized about the dilated blood vessels (Fig. 6).

SULZBERGER-GARBE SYNDROME [11]

Since the Sulzberger-Garbe syndrome was described under the title of "Distinctive Exudative Discoid and Lichenoid Chronic Dermatosis" in 1937, numerous cases

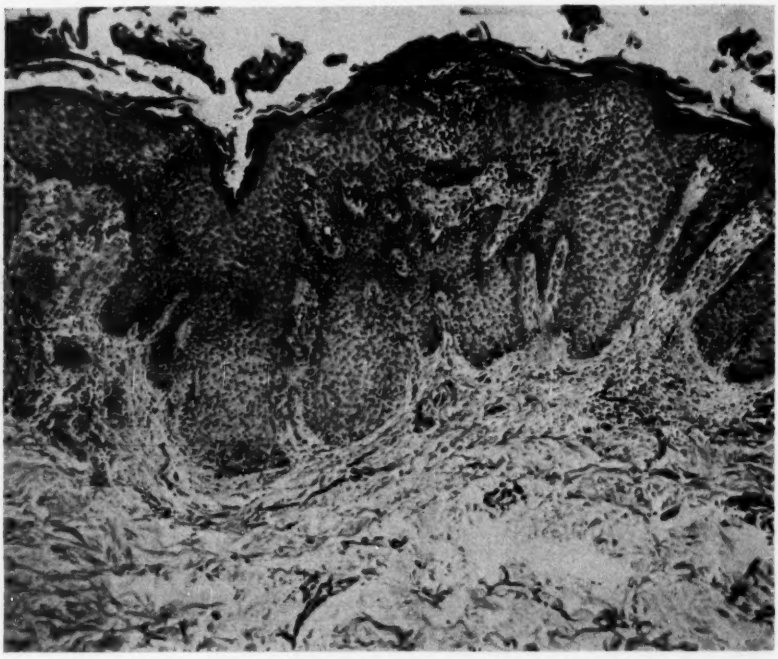

Fig. 6.—Section from a lesion of lichenificatio gigantea developing as part of a phase of Sulzberger-Garbe syndrome. The penetrating epithelial pegs, the broadened papillae, and the hyperkeratosis are evident.

have been observed and recorded. Sulzberger and Garbe could distinguish a series of four phases of lesions, as follows: (1) exudative and discoid, (2) lichenified, (3) premycotic, and (4) urticarial. The exudative and discoid lesions were usually ephemeral, and distinct vesiculation was almost never present. They eventuated in lichenified lesions, either in the form of papules, many of which were follicular, or as diffuse involvement of large tracts of skin, sometimes with generalization. The latter phase was described as the premycotic phase. In the urticarial phase, the authors stated, the lesions resembled "prurigo papules." It is interesting to note

11. Sulzberger, M. B., and Garbe, W.: Nine Cases of a Distinctive Exudative Discoid and Lichenoid Chronic Dermatosis, Arch. Dermat. & Syph. **36**:247 (Aug.) 1937.

the way in which these varying clinical features fit into our concept of atypical variants of lichen simplex chronicus and the way a large portion, at least, of this polymorphous eruption falls into this category.

The disease was described as intractable, associated with maddening pruritus of a nocturnal and paroxysmal character, with localizations frequently about the genitals, mammae, and mouth, and generally unresponsive to the usual modes of dermotherapy. All these features fit in with our concept of psychogenic pruritus.

The alternation of urticaria-like lesions and cutis anserina, with severe, uncontrollable pruritus, and ferocious rubbing and scratching of the skin, are understandable, psychogenically induced phenomena, often reflecting changes in the patient's mood with regard to his emotional problems.[1c] All patients were middle-aged intelligent Jewish men. (Later reports by others included gentiles as well as women.) Furthermore, the authors described their patients as hyperkinetic, cyclothymic, or neurotic personalities. Some of the patients improved with a change of environment, only to relapse when they returned home.

More recently Schneider and Kesten [12] have reviewed the literature on this entity and have suggested the apt designation "polymorphic prurigo." They concluded that emotional factors play a major role in this disease and that psychiatric treatment is the most effective method of handling this problem.

We have also felt that this disease is largely a cutaneous manifestation of a deep-seated emotional disturbance and have had some success when proper psychiatric help could be obtained.

Sachs and Kirsch,[13] in a histopathologic study of 13 cases of this entity, state that the picture is distinctive, that "it often simulates a neurodermatitic reaction but with plasma cells in the infiltrate." They state, however, that the amount and regularity of the acanthosis is not constant, nor is the degree of edema, and that "the many clinical variations of this dermatitis are due entirely to changes in the epidermis."

SUMMARY

1. Lichen simplex chronicus, prurigo nodularis, lichenificatio gigantea, and certain phases of the Sulzberger-Garbe syndrome are closely related clinical and histopathological processes.

2. All these syndromes are characterized fundamentally by the presence of lichenification in various stages of development and modification.

3. Lichenification is a cutaneous reaction to rub-and-scratch trauma to the skin. Frequently this trauma is the somatic manifestation of an emotional disturbance.

4. There are at least 14 characteristics associated with emotionally induced lichenification which are of aid in its etiologic identification.

5. Our observations lead us to believe that these different expressions of emotionally induced lichenification can be accounted for on the basis of an acceptable psychodynamic mechanism.

1825 Pine St.

255 S. 17th St.

12. Schneider, E., and Kesten, B.: Polymorphic Prurigo: A Psychosomatic Study of 3 Cases, J. Invest. Dermat. **10**:205 (March) 1948.

13. Sachs, W., and Kirsch, N.: Exudative Discoid and Lichenoid Chronic Dermatosis (Sulzberger-Garbe): Histopathologic Study, J. Invest. Dermat. **8**:215 (April) 1947.

PRIMARY INVOLVEMENT OF THE UPPER EXTREMITIES IN THROMBOANGIITIS OBLITERANS

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AND
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SAN FRANCISCO

THROMBOANGIITIS obliterans (Buerger's disease), limited primarily to the upper extremities, is rarely seen. Recently we have observed two patients with this disease of the upper extremity, neither of whom had clinical evidence of involvement of the lower extremities. In both patients painful ischemic ulcers of the finger tips developed. The lesions became infected and were treated as pyodermas until underlying vascular disease was recognized.

In typical cases of thromboangiitis obliterans, 40% of the patients suffer from arterial disease of the upper extremities in association with occlusive arterial disease of the lower extremities.[1] It is unusual for the disease to develop in the hands clinically before there are symptoms referable to the legs.[2] Constam reviewed the clinical findings of 94 patients with the disease and reported that in four of this group signs and symptoms of thromboangiitis obliterans of the upper extremities developed before the lower extremities were involved.[3]

From 1935 to 1949 there were 51 patients with thromboangiitis obliterans studied at the outpatient department of Stanford University Hospitals. Three of these patients had involvement of the hands primarily. Recently two additional patients were observed with involvement of the upper extremities alone. We are reporting these two cases because thromboangiitis obliterans of the hands is frequently unrecognized.

REPORT OF CASES

CASE 1.—A 45-yr.-old white American butcher complained of an infection of the right middle finger. For eight years he had noted increased pallor of his hands on exposure to cold, followed by extreme redness. During the past four years cramping pains developed in his hands when he was cutting meat or when his hands were cold. In the past three months cold air or grasping a cold steering wheel resulted in painful blanching of his hands. In the past year the patient observed that the skin around his finger-nails was particularly dry, fissured easily, and healed slowly. He had smoked 40 to 60 cigarettes daily for approximately 20 yr. There was no

1. Allen, E. V.; Barker, N. V., and Hines, E. A., Jr.: Peripheral Vascular Disease, Philadelphia, W. B. Saunders Company, 1946.

2. Allen, E. V.: Thrombo-Angiitis Obliterans: Methods of Diagnosis of Chronic Occlusive Arterial Lesions Distal to the Wrist with Illustrative Cases, Am. J. M. Sc. **178**:237-244, 1929. Buerger, L.: Concerning Vaso-Motor and Trophic Disturbances of the Upper Extremities, with Particular Reference to Thrombo-Angiitis Obliterans, ibid. **149**:210-229, 1915. Campbell, K. N.; Harris, B. M., and Coller, F. A.: Follow-Up Study of Patients with Thrombo-Angiitis Obliterans, Surgery **26**:1003-1013, 1949. Hamlin, E., Jr.; Warren, R., and Kennard, H.: Thromboangiitis Obliterans, New England J. Med. **241**:849-853, 1949. Barker, N. W., and Hines, E. A., Jr.: Arterial Occlusion in the Hands and Fingers Associated with Repeated Occupational Trauma, Proc. Staff Meet., Mayo Clinic **19**:345-349, 1944.

3. Constam, G. R.: Primary Involvement of the Upper Extremities in Thrombo-Angiitis Obliterans, Am. J. M. Sc. **174**:530-536, 1927.

history of phlebitis or of intermittent claudication of the lower extremities. Four weeks before entry an ulcer appeared on his right middle finger; it gradually increased in size and did not respond to local treatment.

On examination a sharply demarcated, superficial, ischemic, exquisitely tender ulcer was present on the tip of the right middle finger. The lesion measured 1 by 1 cm. and was surrounded by a zone of erythema. The finger-nails of both hands were thickened and brittle. The digital pads of the fingers were pitted and taut. His hands were cold to palpation and had a bluish-red color. There was marked elevation pallor and dependency rubor of the hands. Pulsations of the ulnar arteries were absent bilaterally, and pulsations of the radial arteries were diminished. There was no evidence of local pressure on the subclavian artery. Pulsations of the femoral, popliteal, dorsalis pedis, and posterior tibial arteries were easily palpable; no elevation pallor or dependency rubor of the feet was present. His feet were not infected by mycotic disease. The blood pressure was 116 mm. of mercury systolic and 62 mm. of mercury diastolic.

Laboratory examination of the blood revealed a normal hematocrit reading, hemoglobin content, red blood cell count, and white blood cell count. Blood urea and blood cholesterol were

Fig. 1 (Case 1).—Localized blanched areas and superficial exquisitely painful erosion on the tip of the right middle finger.

within normal limits. A serologic test for syphilis elicited a negative reaction. Results of urine examination were normal. There was no evidence in the roentgenograms of arterial calcification of the hands or feet, and the electrocardiogram was normal.

Bilateral upper thoracic sympathectomy was performed. After the operation there was rapid and progressive improvement and healing of the ulcer. At the patient's insistence repair of Dupuytren's contracture of the left palm was performed. At the time of surgery it was noted that the interdigital arteries and the superficial palmar arch did not pulsate. Two months after surgery the ulcer had healed completely and the patient was free of pain.

CASE 2.—A 33-yr.-old white Polish electrician had a small painful ulcer on his left index finger which developed after slight trauma four months before entry. The ulcer did not heal and became increasingly painful. Two months after the appearance of this ulcer a second ulcer appeared spontaneously on his right third finger. There was no history of any serious illness. For the past five years the patient had noticed pallor of the skin of his hands following exposure to cold. He smoked five to six cigars and 20 to 30 cigarettes daily. During the past 18 mo. he

complained of cramping pains in his hands while at work. He had no symptoms referable to the lower extremities and no history of phlebitis.

On physical examination an ischemic ulcer 4 mm. in diameter was observed at the tip of the left index finger. An identical ulcer was present at the tip of the right middle finger. The fingers were cold to palpation and were of a reddish-cyanotic hue. No cutaneous sclerosis was present. There were elevation pallor and dependency rubor of the hands. The ulnar artery pulsations were absent. Pulsations of the radial artery were of normal amplitude. There was no evidence of local compression of the subclavian artery. Arterial pulsations of the lower extremities were normal. The blood pressure was 140 mm. of mercury systolic and 84 mm. diastolic.

Laboratory studies revealed the blood and urine to be normal, and serologic reactions for syphilis were negative. The patient was hospitalized for three weeks. Treatment consisted of bed rest, applications of antibiotics, and abstinence from tobacco. Approximately four months after he was first seen, the ulcer had healed and his pain had disappeared.

COMMENT

The criteria for the diagnosis of thromboangiitis obliterans are evidence of occlusive arterial disease; color changes with elevation pallor and dependency rubor;

Fig. 2 (Case 2).—Dull, lusterless, and brittle nails; vasospasm of the third finger.

vasomotor phenomena; increased sensitivity to cold; pain which is accentuated by exercise and which may be present at rest in the late stages of the disease, and minor trophic changes that may progress to gangrene. Migratory thrombophlebitis occurs in approximately 20 to 25% of the patients with this disease and, when present, is of diagnostic significance.[4] Pain may be a prominent feature and usually results from ischemic neuritis. In Case 1 cramps developed in the patient's hands while cutting meat. This pain was relieved by rest. Often it may be difficult to palpate the ulnar or radial artery and determine the presence of occlusive arterial disease. The Allen test is useful to determine the patency of these vessels.[1] A history of excessive use of tobacco is important. Allen, Barker and Hines[1] state in their texbtook: "Only a very few isolated cases of thrombo-angiitis obliterans

4. Buerger, L.: The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924, p. 214.

have been reported in nonsmokers. We have known one case which was proved pathologically, two probable cases as judged by clinical evidence, and two questionable cases during a fifteen-year period at the Mayo Clinic." Evans and Silbert have written emphasizing the etiologic role of tobacco in this disease.[5] The high incidence of the disease in males (99%) seems to be of etiologic significance.

The diagnosis of thromboangiitis obliterans of the digital type was made in these two cases on the following evidence: organic occlusion of a medium-sized artery, Raynaud's phenomenon, intermittent pain of the hands, and presence of superficial painful ulcers.

DIFFERENTIAL DIAGNOSIS

There are many causes of ulcers of the finger-tips. Primary Raynaud disease when of long standing and unusual severity may cause ulcerative lesions. However, Raynaud's disease may easily be differentiated from thromboangiitis obliterans by the absence of occlusive arterial changes.[6] Scleroderma of the acrosclerotic type is recognizable by the tautness and induration of the affected skin. Also scleroderma seldom causes occlusion of arterial pulsations in the wrist. There is rarely elevation pallor or dependent rubor of the hands of patients with primary Raynaud disease or scleroderma, as one finds in the hands of patients with thromboangiitis obliterans. Occasionally there is loss of skin with subsequent superficial erosion in neurovascular lesions.[7] Neurovascular syndromes of the shoulder girdle, such as cervical rib syndrome, scalenus anticus syndrome, hyperabduction syndrome, and costoclavicular syndrome, must be considered in the differential diagnosis.[8] Small punched-out ulcers and Raynaud's phenomena may occur in pneumatic hammer disease,[5b] ergotism, acute arterial occlusion, post-traumatic arterial occlusion, and arterial embolism. Ulcers of the finger-tips without Raynaud's phenomena may be caused by local inflammatory processes, frostbite, and syringomyelia. X-ray and radium, when handled without proper precautions, have not infrequently caused ischemic ulceration of the fingers. Localized granulomas, mycotic and infectious, neoplasms, and blood dyscrasias occasionally produce small ulcers on the finger-tips, but usually lesions appear on other parts of the integument.

It is not within the scope of this paper to discuss therapy of thromboangiitis obliterans. Methods of treatment are discussed in numerous excellent reviews.[9]

SUMMARY

Two patients with digital thromboangiitis obliterans of the upper extremity have been studied. Early recognition of this disease as a cause of ulceration of the digits of the hands is important because early recognition with adequate treatment may prevent the loss of a finger or a limb.

5. (*a*) Evans, W. F., and Stewart, H. J.: The Effect of Smoking Cigarettes on Peripheral Blood Flow, Am. Heart J. **26**:78-91, 1943. (*b*) Silbert, S.: Etiology of Thromboangiitis Obliterans, J. A. M. A. **129**:5-9 (Sept. 1) 1945.

6. Allen, E. V., and Brown, G.: Raynaud's Disease: A Critical Review of Minimal Requisites for Diagnosis, Am. J. M. Sc. **183**:187-201, 1932.

7. Lewis, T., and Pickering, G. W.: Circulatory Changes in the Fingers of Some Diseases of the Nervous System, with Special Reference to the Digital Atrophy of Peripheral Nerve Lesions, Clin. Sc. **2**:149-185, 1935.

8. Wright, I. S.: Vascular Disease in Clinical Practice, Chicago, The Year Book Publishers, Inc., 1948.

9. Allen, Barker, and Hines.[1] Linton, R. R.: Peripheral Vascular Diseases, New England J. Med. **240**:645-654, 1949. Peripheral Vascular Disease, Am. J. Med. **5**:433-448, 1948. Wright.[8]

FIXED DRUG ERUPTION FROM AUREOMYCIN

Report of Two Cases

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CINCINNATI

WE HAVE been unable to find any reference in the literature to a fixed type of eruption from any of the antibiotics. The literature includes reports of reactions of various types to aureomycin,[1] but in no instance is the fixed type of eruption described.

1. Finland, M.; Collins, H. S., and Paine, T. F., Jr.: Aureomycin, a New Antibiotic: Results of Laboratory Studies and of Clinical Use in 100 Cases of Bacterial Infections, J. A. M. A. **138**:946 (Nov. 27) 1948. Lennette, E. H.; Meiklejohn, G., and Thelen, H. M.: Treatment of Q Fever in Man with Aureomycin, Ann. New York Acad. Sc. **51**:331 (Nov. 30) 1948. Meiklejohn, G., and Shragg, R. I.: Aureomycin in Primary Atypical Pneumonia: A Controlled Evaluation, J. A. M. A. **140**:391 (May 28) 1949. Riese, J. A.: Toxic Reaction to Aureomycin: Report of a Case, J. M. Soc. New Jersey **46**:467 (Oct.) 1949. Rosanova, A. R., and Warszewski, E.: Skin Rash from Aureomycin, M. Times, New York **77**:524 (Nov.) 1949. Harris, H. J.: Aureomycin and Chloramphenicol in Brucellosis, with Special Reference to Side Effects, J. A. M. A. **142**:161 (Jan. 21) 1950. Brackstone, L. B.: Aureomycin, Mississippi Doctor **27**:424 (Feb.) 1950. Vitamin Deficiency and Antibiotics, Correspondence, Brit. M. J. **1**:491 (Feb. 25) 1950. Weyler, H. L. C.: Skin Irritation Around the Anus Due to Aureomycin, Rhode Island M. J. **33**:137 (March) 1950. Herrell, W. E.: Clinical Experience with the Newer Antibiotics, Bull. North Shore Branch, Chicago M. Soc. 7 (March) 1950. Robinson, H. M., Sr.: Aureomycin in Treatment of Some Dermatoses, Arch. Dermat. & Syph. **61**:384 (March) 1950. Downing, J. G.: Medical Progress: Dermatologic Therapy, New England J. Med. **242**:546 (April 6) 1950. Tzanck, A.; Sidi, E., and Habault: Un cas d'intolerance a l'aureomycine, Presse méd. **58**:396 (April 8) 1950. Peck, S. M., and Feldman, F. F.: Sensitivity Reactions to Aureomycin, J. A. M. A. **142**:1137 (April 15) 1950. McVay, L. V., Jr.; Laird, R. L., and Sprunt, D. H.: The Treatment of Amebiasis with Aureomycin, South. M. J. **43**:308 (April) 1950. Parets, A. D.: Angioneurotic Edema and Rash Due to Aureomycin: Reaction in a Patient with Multiple Sensitivities, J. A. M. A. **143**:653 (June 17) 1950. Downing, J. G.: Black Tongue as a Result of Antibiotic Therapy: Report of a Case, New England J. Med. **242**:1013 (June 29) 1950. Burstein, F.: Sensitivity to Aureomycin: Report of a Case, Am. J. Ophth. **33**:973 (June) 1950. Hickey, C. S.: General Reactions Following the Use of Aureomycin in the Eye, J. Maine M. A. **41**:282 (July) 1950. Shaffer, J. M.; Bluemle, L. W., Jr.; Sborov, V. M., and Neefe, J. R.: Studies on the Use of Aureomycin in Hepatic Disease: IV. Aureomycin Therapy in Chronic Liver Disease, with a Note on Dermal Sensitivity, Am. J. M. Sc. **220**:173 (Aug.) 1950. Black Tongue from Aureomycin, Correspondence, J. A. M. A. **143**:1514 (Aug. 26) 1950. Geographic Tongue, Queries and Minor Notes, ibid. **144**:598 (Oct. 14) 1950. Lewis, C. S., Jr.; Bauerlein, T. C., and Shytles, H. M., Jr.: Effect of Aureomycin on the Stomach: A Gastroscopic Study, Gastroenterology **16**:586 (Nov.) 1950. Galt, J., and Hunter, R. B.: The Effect of Aureomycin on Certain Liver Function Tests and Blood Coagulation, Am. J. M. Sc. **220**:508 (Nov.) 1950.

One of us (A. W.) personally experienced a fixed type of eruption from aureomycin.

REPORT OF CASES

In 1944, A. W. had an urticarial eruption as a result of taking sulfadiazine. In the five years preceding this episode, this drug and other sulfonamides were taken five or six times without reaction. Years before, pruritus without eruption and gastric upsets were produced by acetylsalicylic acid.

The patient had an upper-respiratory-tract infection with sinusitis in the spring of 1949 for which he took 250 mg. of aureomycin every six hours for 14 days. This same course of treatment was taken for the same infection in the fall of 1949 and again in the spring of 1950. No untoward reactions of any type were produced by the first two courses of aureomycin. The third was accompanied with a slight diarrhea.

In November, 1950, he took 250 mg. of aureomycin four times daily, together with one or two aminopyrine (pyramidon®) tablets daily. After three days pruritus developed. Both drugs were continued. After one more day nine red macules appeared, each about 1 to 2 cm. in diameter. One was located in the left temple area, one near the inner canthus of the right eye, one on the dorsal surface of the distal phalanx on the radial side of the right thumb, two on the perineum, one at the base of the penis on the right side, one in the central pubic area, and one in each inguinal area.

The drugs were continued, and after 24 hr. each of the skin lesions became bluish-purple in the center and developed a central bulla which became hemorrhagic. Aureomycin and aminopyrine were discontinued. The lesions faded in seven to 10 days, leaving a brown-pigmented macule at the site of each lesion. It was suspected that the eruption was caused by aminopyrine.

Aureomycin was again taken in mid-December, 1950, and the pigmented macules, which remained after the first eruption, became pruritic, then red, and in 24 hr. bullous. Several were hemorrhagic. This reaction occurred after the ingestion of three of the 250-mg. capsules of aureomycin. Aminopyrine was not taken. This eruption faded in 10 days. Aminopyrine, two tablets daily, was taken for two days. There was no change in the pigmented macules. Accordingly, aureomycin was suspected as the cause of the eruption.

On Jan. 6, 1951, he ingested 25 mg. of aureomycin (spersoids®). Within 30 min. pruritus developed on each of the pigmented sites of the former eruption, and it became generalized during the next half-hour. An additional 25-mg. dose of aureomycin was taken, and within an hour the sites of the former eruption became red and bullous. Diarrhea occurred three hours after ingestion of the second dose of aureomycin and continued for 24 hr. The eruption faded in 14 days, but dark-brown pigmented macules remained.

No other drug was taken during the last two intervals that aureomycin was ingested. Penicillin and terramycin were taken before and since the appearance of the fixed eruption. These drugs produced no reaction.

The second episode of this eruption was shown to several dermatologists at a meeting of the staff of the department of dermatology of the Cincinnati General Hospital. One of us (L. G.) stated that he had a patient under study, who had what appeared to be a similar eruption. A report of this case follows:

G. C., a 64-yr.-old man, was seen on Dec. 19, 1950. He had been taking aureomycin since Dec. 17 because of a recurrence of a pulmonary infection. (This patient has severe asthma and a known sensitivity to sulfonamides.) He presented purple-red, annular lesions on the face and neck of 24 hr. duration. These lesions appeared at the sites of pigmented, macular areas which were residual of erythema multiforme lesions, which had appeared in these areas on Oct. 11, 1949. The cause of this eruption was unknown but was suspected of having an infectious basis. The presenting lesions were extremely pruritic and exhibited a mild degree of edema in several areas. This eruption faded in eight days, leaving the brown pigmented macules.

On Dec. 30 the patient was given ten 15-mg. tablets of aureomycin at three-hour intervals. There was no associated change in the pigmented macules. On Jan. 3, 1951, he was given three

250-mg. capsules of aureomycin at three-hour intervals. In 24 hr. he had a definite exacerbation of pruritus, increase in erythema, and increase in size of the previously affected areas. No new lesions were noted.

In order that photographs of active lesions could be taken, this patient was again given four 250-mg. capsules of aureomycin on Jan. 21. On this occasion the pruritus occurred six hours after ingestion of the fourth capsule, and within 12 hr. all the previous pigmented lesions were inflamed and edematous.

The following investigative procedures were done on these two patients: (*a*) Patch tests with aureomycin ointment and with a 3% solution of aureomycin on normal skin areas elicited negative reactions. (*b*) Intradermal tests with intravenous solution of aureomycin on normal skin areas elicited negative reaction. (*c*) Intradermal tests with this solution on affected sites also elicited negative reaction. (*d*) Reaction to a control test with this solution on another person was negative.

A negative reaction to intravenous solution of aureomycin is described as follows: A marked burning sensation occurs immediately on injection, and within a few minutes an area of erythema about 3 cm. in diameter appears. (Both patients experienced less burning when the test was done on the affected site than when it was done on the normal skin.) In two hours the immediate erythematous reaction disappears, and an erythematous, edematous papule about 0.5 cm. wide by 0.25 cm. high is left. This papule remains about seven days. The same type of reaction occurred in normal skin areas and affected sites in both patients and in the control.

COMMENTS

The first case appears to represent a classic fixed type of drug eruption produced by aureomycin. In the second case a fixed type of eruption from aureomycin appears to have developed at the sites of pigmented areas, the pigment representing a residual in the skin from a former eruption, due to an entirely unrelated cause. It is interesting to note that both of these patients had sensitivities to sulfonamides. There are many reports of eruptions appearing on areas of skin previously sensitized by topical application of various antibiotics when the same antibiotic was subsequently given parenterally. There are other reports describing several types of eruptions, varying from urticaria to generalized exfoliative dermatitis, resulting from parenteral administration of the antibiotics.

SUMMARY

The cases described in this report appear to represent a fixed type of drug eruption produced by aureomycin.

441 Vine St.

19 Garfield Pl.

Clinical Notes

PERIARTERITIS NODOSA

Report on a Patient Treated with Paraaminosalicylic Acid

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DETROIT

Until recently periarteritis nodosa has been considered a rare disease. The number of cases on record has increased considerably. This apparent increase has resulted from the attention clinicians and pathologists have given the disease. The dermatologist is in an especially good position to diagnose periarteritis nodosa when it shows itself in the skin.

Cutaneous manifestations vary from simple erythema to erythema multiforme or erythema nodosum, urticaria, and even purpura. Subcutaneous nodules develop which occasionally are followed by vesicular, pustular, or necrotic lesions, depending on the size of the vessel involved and the situation and depth of the nodule. Lesions may be single or multiple. They occur as nodules along the course of a superficial artery. The lesions are usually very painful on pressure. Systemic manifestations are multiple and protean and may pertain to any organ of the body and, again, are dependent on the amount of vascular damage done. The general picture in periarteritis nodosa is that of subacute illness with remission and acute exacerbation generally associated with irregular fever, tachycardia, weakness, and acute pains in various regions. Eosinophilia is commonly present. The disease may progress rapidly and terminate fatally within a few weeks, but many cases have been described recently in which the disease lasted for many years. Several have been reported in which recovery occurred.[1]

We believe the case of periarteritis nodosa under study is of particular interest since a relatively new therapeutic agent, paraaminosalicylic acid has seemingly arrested the progress of the disease. Paraaminosalicylic acid has shown some promise in the management of another collagen disease, lupus erythematosus disseminatus.[2] It was decided, therefore, to try the drug in the treatment of this patient with periarteritis nodosa.

REPORT OF CASE

The patient, J. F., a 58-yr.-old white man, presented himself for the first time to one of us (L. C.) in September, 1949. He complained of a burning, somewhat painful, itching eruption on the legs and feet. The patient stated that it began about three months earlier as a small "pimple" over the right shin. He scratched it, producing an ulcer. This area scabbed over and later ulcerated. The lesion was not improved by self-medication with various ointments. About three weeks prior to the patient's first visit small "blisters" began to spread over the right leg and foot. Some of these later developed into scabs and others appeared to the patient as areas of "bleeding into the skin." Similar lesions appeared on the left leg and foot. The patient complained of general weakness and difficulty in walking up stairs.

Dr. Carrick is from the Department of Dermatology and Syphilology, Wayne University College of Medicine and City of Detroit Receiving Hospital, Loren W. Shaffer, M.D., Chairman. Dr. Vonder Heide is Associate Director, Department of Clinical Investigation, Parke, Davis & Company.

1. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1948.

2. Hendren, O. S.: in discussion of Cases of Treatment with Paraaminosalicylic Acid, Arch. Dermat. & Syph. **62**:753 (Nov.) 1950.

The skin of the lower third of both legs and feet exhibited pinhead- to pea-sized necrotic ulcers in some areas and red to purple hemorrhagic lesions, vesicles, and bullae in others. The largest crusted ulcer measured 3 cm. in diameter and was located over the right pretibial region (Fig. 1). Some of the lesions were very tender. No eruption was seen elsewhere on the body. The patient was tall but poorly developed. General physical examination by systems showed nothing significant. Blood pressure was 100 systolic and 64 diastolic.

A punch biopsy specimen was taken from the edge of the largest ulcer on the right leg. The dermatopathologist (Dr. Hermann Pinkus) reported that the sections showed almost complete loss of the epidermis. Part of the surface was covered with a serous crust or dried bulla under which some thin epidermis was present; the greater extent was occupied by fairly deep-reaching necrosis. The corium contained thick-walled blood vessels surrounded by infiltrate

Fig. 1.—Lesions of periarteritis nodosa before treatment.

which was about two-thirds eosinophilic leucocytes. The vascular walls often showed necrosis of "fibrinoid" degeneration. There were free red blood cells in the corium. He concluded that because of the vascular changes and eosinophilia, he believed that this was a case of periarteritis nodosa.

Hematologic studies by Dr. Vonder Heide showed erythrocytes, 4,450,000; hemoglobin, 82% (13.6 gm.); thrombocytes, 150,000; capillary fragility, normal; leucocytes, 5,250; neutrophils, stab, 5%; neutrophils, segmented, 43%; eosinophils, 4%; lymphocytes, 41%; monocytes, 7%; moderate thrombocytopenia; lymphocytosis with toxic changes in all neutrophils; and slight eosinophilia. Urinalysis showed albumin present; sugar normal; reaction, alkaline; specific gravity, 1.020. On microscopic examination many casts, finely granular, amorphous phosphates, a few epithelial cells, and pus cells (1 to 2 per high power field) were seen. The reaction to the serologic test (Kahn) for syphilis was negative.

Treatment.—As soon as the diagnosis of periarteritis nodosa was established the patient was given pamisyl® [3] (0.5 gm. of paraaminosalicylic acid) by mouth, one tablet four times a day on the first day, two tablets four times a day on the second day, and so on, the dose being increased by four tablets each day until a maximum maintenance dose of six tablets four times a day was reached. This daily maintenance dose of 12 gm. pamisyl® was continued without interruption for a total of 12 mo. No local therapy was used except the occasional application of 2% diphenhydramine cream as needed to control pruritus.

Course.—Examination of the skin 10 days after the start of therapy with pamisyl® revealed some healing of the ulcers, and the vesicles and bullae were beginning to involute. During the following eight months of therapy the lesions gradually disappeared and only a few hemorrhagic macules remained. Except for postinflammatory hyperpigmentation, the skin of both legs and

Fig. 2.—Skin after 11 mo. treatment with pamisyl.®

feet was completely normal in appearance after 11 mo. of therapy (Fig. 2). The administration of pamisyl® was continued another six weeks, and then the dose was reduced by one-half. After three weeks of taking the lower dosage vesicles and bullae began to develop on the legs and feet. The dose was then increased again to 12 gm. of pamisyl® daily, and, after three weeks of this higher dosage, the lesions disappeared. During the course of treatment the patient gradually gained strength, and at the time the final photographs were taken (11 mo. after beginning treatment) he was able to climb stairs easily and had been painting his house and standing on a ladder without any difficulty. At no time during the course of treatment did the patient lose time from his work as a parts-inspector in an automobile factory. There were no complications from the use of pamisyl® except occasional loss of appetite.

3. Supplied for clinical trial by Parke, Davis & Company, Detroit.

Hematologic findings after 11 mo. of treatment showed erythrocytes, 4,440,000; hemoglobin, 88% (a gain of 6%); thrombocytes, 220,000 (a rise of 70,000); neutrophils, stab, 7%; neutrophils, segmented, 45%; eosinophils, 2% (a drop of 2%); lymphocytes, 35% (a drop of 6%); monocytes, 9%; slight normochromic and normocytic anemia; moderate lymphocytosis and monocytosis; and some toxic changes in the lymphocytes. Urinalysis showed reaction, acid (reversed from alkaline); specific gravity, 1.016; albumin, negative (reversed from positive); sugar, normal; pus cells (0 to 2 per high power field); a few epithelial cells; and no casts or crystals.

SUMMARY

Lesions of cutaneous periarteritis nodosa completely involuted in 11 mo. with paraaminosalicylic acid (pamisyl®) therapy. It is hoped that this case presentation will stimulate further interest in the use of pamisyl® in periarteritis nodosa.

TRIAL OF SOME ADENOSINE COMPOUNDS IN PRURITUS

CARL M. PEARSON, M.D.
AND
JOHN L. FROMER, M.D.
BOSTON

Generalized or localized pruritus is a symptom frequently encountered in medical and dermatologic practice. It is evident from the large number of therapeutic remedies which have been applied both locally and systemically in pruritus that no single means of controlling itching in the majority of these cases is available.

Within the past two years several reports [1] have appeared which have indicated that the parenteral administration of adenylic acid (adenosinemonophosphate) may be of value in the relief of pruritus from many different causes. On the basis of these results, the suggestion has been made [1b] that there may be a fundamental mechanism for pruritus which involves the metabolism of adenylic acid.

Recently we have had an opportunity to observe the effect of adenylic acid and a related compound, adenosinetriphosphate, on a series of patients with pruritus originating from a variety of conditions, chiefly dermatologic. In general, the results of these studies have been disappointing. Several of the patients claimed varying degrees of relief of itching following intramuscular injections of these substances, but the majority experienced little or no relief and a few even thought that their symptoms were intensified.

The preparations used were muscle adenylic acid (adenosine-5-phosphoric acid),[2] 20 mg. per cubic centimeter in a neutral buffered solution, and adenosinetriphosphate, 25 mg. per cubic centimeter, also in a neutral buffered solution. All the injections were given intramuscularly and in varying dosages, but most frequently 20 mg. of adenylic acid and 25 mg. of adenosinetriphosphate every six hours. A few patients received hourly injections for five consecutive hours each day, as suggested by Rottino,[1b] but no advantage was noted by use of this procedure. No adverse reactions were noted on this dosage schedule except for occasional transient discomfort at the site of injection. Most other forms of adjuvant therapy for dermatitis and pruritus were withheld during the initial trial period.

The results of treatment in 26 cases are presented in Tables 1 and 2. As can be seen, the majority of patients with true dermatologic conditions, as well as those with "idiopathic"

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1. (*a*) Rottino, A.: Relief from Pruritus Following upon Administration of Adenylic Acid, Proc. Soc. Exper. Biol. & Med. **71**:379-381 (July) 1949; (*b*) Effect of Adenylic Acid Therapy upon Pruritus Due to Hodgkin's and Other Diseases, Cancer **3**:272-278 (March) 1950. (*c*) Kennedy, R. J.: The Treatment of Pruritus with Adenosine-5-Monophosphate (Muscle Adenylic Acid), New York State J. Med. **50**:1609-1610 (July) 1950.

2. The adenylic acid was lycedan® and the adenosinetriphosphate was tripadene,® both made by and supplied through the courtesy of Schwarz Laboratories Inc., New York.

pruritus, derived slight or no relief from the administration of the adenosine compounds and several noticed an intensification of itching while under treatment. There was little or no difference in the effect of adenylic acid and adenosinetriphosphate upon pruritus in the several cases in which these substances were consecutively administered to the same patient.

TABLE 1.—*Results of Administration of Adenylic Acid*

Case	Age	Sex	Disease	Total Dose, Mg.	Results *
1	45	F	Atopic dermatitis	700	0
2	20	F	Atopic dermatitis	1,400	2+ (transient)
3	40	M	Atopic dermatitis	1,100	0 †
4	24	M	Atopic dermatitis	600	0
5	68	M	Neurodermatitis	600	0
6	48	F	Acute dermatitis	400	Worse
7	61	M	Exfoliative dermatitis	300	0
8	55	M	Exfoliative dermatitis	480	0 or worse
9	24	M	Chronic urticaria	490	0
10	55	F	Acute urticaria (penicillin)	350	0
11	40	F	Erythema multiforme	700	0
12	33	M	Pruritus ani	500	0 or worse
13	54	F	Pruritus ani et vulvae	800	1+ (transient)
14	35	F	Hodgkin's disease	400	1+ (transient)
15	61	F	Chronic myelogenous leukemia	1,000	3+ ‡
16	29	F	Stasis dermatitis	500	4+ §
17	52	M	Stasis dermatitis	600	3+

* 4+ means complete relief from pruritus.
† Seemed to improve for two days, then had a severe acute recurrence of dermatitis while under treatment.
‡ Improvement lasted about three weeks and then pruritus recurred; no further opportunity to treat.
§ This patient noted complete relief of itching and slight relief of accompanying pain for three months after treatment.

TABLE 2.—*Results of Administration of Adenosinetriphosphate*

Case	Age	Sex	Disease	Total Dose, Mg.	Results *
18	44	F	Atopic dermatitis	1,100	1+ (transient)
19	20	M	Atopic dermatitis	700	0
20	20	M	Atopic dermatitis	800	0
21	47	F	Neurodermatitis	700	0
22	50	F	Acute urticaria (penicillin)	400	1+
23	33	M	Pruritus ani	400	0
24	45	F	Pruritus ani et vulvae	700	3+
25	38	F	Pruritus ani et vulvae	500	1+
26	44	M	Jaundice (infectious hepatitis)	500	3+ †

* 4+ means complete relief from pruritus.
† Improvement was noted concurrent with a slowly decreasing intensity of icterus.

In general, it appears that pruritus accompanying many dermatologic conditions responds poorly to medication with the adenosine compounds. On the other hand, mild improvement was noted in the two cases of lymphoma with associated pruritus, although the favorable response was rather brief in duration. In two cases of varicose ulceration of the ankles with stasis dermatitis associated with pain and intense pruritus, the itching subsided completely and the pain partially in each case. The latter observation coincides with the preliminary observations made

by Rottino, Boller, and Pratt.[3] There was no indication in these cases that the rate of healing of the skin ulcerations was accelerated.

In general, the lack of antipruritic effect of these compounds in our cases is in direct contrast to the results reported by several other workers. Rottino [1b] has obtained most effective results in cases of Hodgkin's disease with pruritus, but in his series he has also included a fairly large number of cases of "idiopathic" pruritus as well as some of pruritus associated with diabetes and sensitization dermatitis. In most of these cases he observed a consistently satisfactory result. In contrast, he has treated very few pruritic dermatoses, which have provided the bulk of our series. Kennedy [1c] has reported on a series of four patients who derived relief from pruritus in several conditions, two of which were a sensitization dermatitis and two of the "idiopathic" variety. Concurrent local adjuvant therapy was used in some of these cases.

The theoretical possibilities for application of the adenosine compounds in a variety of disease processes are great.[4] They are normal constituents of all body cells and form the basis for several important intracellular enzyme systems, as well as providing building blocks for the highly important nucleic acids. Peters and Thompson [5] have discussed the importance of adenosinetriphosphate in several of the complex enzyme systems in the skin.

The suggestion that pruritus results from a deficiency in adenylic acid or a related compound does not seem to be borne out in our series, and we have not found it to be of sufficient value to continue its administration in similar cases. If such a deficiency does exist, however, the parenteral administration of these substances has not been effective in correcting the deficiency in the cells of the affected skin or in relieving the pruritus to any significant degree. Perhaps some of the noted effects in a few of the cases were due to the known vasodilating action of these substances.

SUMMARY

Adenosine compounds (adenylic acid and adenosinetriphosphate) were administered parenterally to a total of 26 patients suffering from pruritus caused by a variety of conditions, chiefly dermatologic.

The previously reported antipruritic effects of these substances could not be confirmed in the majority of our cases, and the suggestion that there may be a fundamental mechanism for pruritus which involves the metabolism of adenylic acid was not borne out.

605 Commonwealth Ave.

3. Rottino, A.; Boller, R., and Pratt, G. H.: Therapeutic Action of Muscle Adenylic Acid on Ulcers and Dermatitis Associated with Varicose or Phlebitic Veins: Preliminary Report, Angiology **1**:194-200 (April) 1950.

4. Stewart, E. D.: Adenine Compounds: Their Chemical, Physiological, and Therapeutic Properties, J. Am. Pharm. A. (Scient. Ed.) **38**:3-9 (Jan.) 1949.

5. Peters, R. A., and Thompson, R. H. S.: Biochemistry of the Skin, in MacKenna, R. M. B.: Modern Trends in Dermatology, New York, Paul B. Hoeber, Inc., 1949, pp. 94-105.

SPONTANEOUS CURE OF TINEA CAPITIS DUE TO MICROSPORON AUDOUINI

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It has been stated repeatedly in the past that tinea capitis due to Microsporum audouini resolves itself spontaneously at the age of puberty. So far as is known, only Livingood and Pillsbury [1] have referred to the possibility of spontaneous cure before puberty. In the clinic

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1. Livingood, C. S., and Pillsbury, D. M.: Ringworm of the Scalp: Prolonged Observation, Family Investigation, Cultural and Immunologic Studies in 130 Cases, J. Invest. Dermat. **4**:43 (Feb.) 1941.

patients in Detroit I had repeatedly observed what seemed to be prepubertal spontaneous cures. Prepubertal children with tinea capitis due to M. audouini and not seen for one or two years would return free of infection with a story that no treatment had been used. It was felt that these observations might be significant, and a method was at hand for gathering evidence to prove that spontaneous cure did occur in patients with tinea capitis before the age of puberty. A group was available for investigation from the survey conducted by Carrick in the Detroit Public Schools in 1945.[2] Most of these children had not been seen for three and one-half to four years, and it was felt that there was a good chance that a number of them might have received little or no treatment. There were 136 children in this group previously proved to have been infected by M. audouini, of whom 109 were reexamined. Each of these children was reexamined under the Wood light to determine the presence or absence of fluorescent hairs. Cultures were not grown since the offending organism had been previously identified during Carrick's survey and in all cases was M. audouini.

During the examination of each child in this follow-up survey, the following questions were asked: 1. Did you have any treatment for your ringworm? 2. Did you visit a doctor to have treatment or did your parents treat you with home remedies? 3. Did you use a salve or a liquid? Do you know the name of it? How long was it used (more or less than one month, two months, three months, six months, or a year)? 4. Did you have x-ray or "light" treatment? Did your hair fall out? In addition, a mimeographed form was given to the child to take home to his parents to be filled out and returned to the school principal, who in turn forwarded the completed forms to the examiner. This form contained essentially the same questions as the patient was asked. Surprisingly enough, the results of questioning both the child and the parents tallied rather well. All information, including the results of Wood's-light examination, clinical status, exact age, and both parents' and children's answers to questions, was entered on an individual card for each patient. The criterion of cure in this group of patients was a negative result of Wood's-light examination.

It was assumed that any child who had received x-ray epilation successfully was in the adequate-treatment category. The difficulty was in deciding what particular duration of local treatment of any type was to be considered adequate therapy. Since routine cures are not usual in under three months with any sort of local treatment, it was decided arbitrarily to consider local treatment of any type of under three months' duration to be inadequate. It must be borne in mind that the vast majority of children in this survey had not been under a physician's care for any longer than a few weeks, the main reliance being placed on home remedies. When any question arose as to length of time of local treatment, that particular child was placed in the adequately treated category. It was felt that 12 yr. of age would be a conservative estimate as to age of puberty.

The results of the survey are presented in the table. As will be noted the children were divided into age groups of from 9 to 17 yr. of age, the nearest birthday being used as the age. The numbers of children in each age group were broken down into those receiving "adequate" and "inadequate" treatment (under three months) and those in turn being divided into "cured" and "failed." Finally, the results were summarized *in toto* and with the children divided into two groups, one of children under 12 yr. of age and one of children over 12 yr. of age.

There were 61 children 12 yr. of age and under. Of this number, 18 were considered to have had adequate treatment and 43 were not. Of the 18 adequately treated patients, 72.2% presented no fluorescent hairs. Of the remaining 27.8%, the majority showed only a very few scattered fluorescent hairs. As a matter of fact, a few actually presented only a single fluorescent hair. Of the 43 inadequately treated patients under 12 yr. of age, 65.1% showed no fluorescent hairs. The remainder of the group of 43 showed findings similar to those in the adequately treated group.

This trend toward apparent spontaneous cure in children under puberty has been noted by Livingood and Pillsbury,[1] who reported 33.6% of the cures in patients lasting for a period of three to 18 mo. These figures of Livingood and Pillsbury[1] include both inflammatory and

2. Carrick, L.: The Epidemiology of Tinea Capitis in Detroit School Children, J. Michigan M. Soc. **45**:347 (March) 1946.

noninflammatory infections. My own figures also include both types of infection. In the present series a rate of approximately 65% of the children cured was obtained, a figure approximately twice that of Livingood and Pillsbury.[1] The main difference in the two series is the fact that in my series a period of three and one-half to four years had elapsed before examination was made.

If these results are significant, the factor of duration of infection would seem to be as important as the onset of puberty. This factor would have to be taken into consideration in evaluation of new treatments, since it would be important to include adequate numbers of children of all age groups.

Results of Wood's-Light Examination in a Group of 109 Children Previously Found to Be Infected with M. Audouini

Age group	9	10	11	12	13	14	15	16	17
No. examined	10	17	14	20	21	16	5	5	1
Adeq. treatment	1	6	5	6	4	5	3	1	0
Adeq. treatment—cured	0	5	3	5	4	4	1	1	0
Adeq. treatment—failed	1	1	2	1	0	1	2	0	0
Inadeq. treatment	9	11	9	14	17	11	2	4	1
Cured	5	8	6	9	14	8	1	3	0
Pos. hair present	4	3	3	5	3	3	1	1	1

Total 12 yr. and under	61	
Adeq. treatment	18	
Cured	13	(72.2%)
Inadeq. treatment	43	
Cured	28	(65.1%)
Total 13 yr. and over	48	
Adeq. treatment	13	
Cured	10	(76.9%)
Inadeq. treatment	35	
Cured	26	(74.3%)
Grand total	109	
Adeq. treatment	31	
Cured	23	(74.2%)
Inadeq. treatment	78	
Cured	54	(68%)

SUMMARY AND CONCLUSIONS

1. Evidence is presented which, if valid, suggests that prepubertal spontaneous cure is possible in tinea capitis due to Microsporum audouini.

2. Duration of infection may be an important consideration in evaluating the efficacy of local treatment in tinea capitis.

VITILIGO IN (APPARENT) DERMATOMAL DISTRIBUTION

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and
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PASADENA, CALIF.

Although the exact mechanisms involved in the causation of primary depigmentation of the skin are not known, the hypothesis of the participation of the nervous system has been considered by many writers, on the basis of indirect clinical evidence. Some cases of vitiligo show absolute (mirror image) bilateral symmetry. This distribution is difficult to explain except on the basis of central nervous system participation, that is, segmental-dermatomal arrangement. However, since the involvement of any one dermatome is usually very incomplete, the fact of dermatomal involvement has not been readily proved. The case reported here brings no final proof but does present what appears to be strong clinical evidence to support the idea that the central nervous system plays a role in the pathogenesis of vitiligo.

REPORT OF A CASE

A 28-year-old white American shoemaker, C. D., was first seen in October, 1949, presenting a large area of pigment loss involving the lower half of the abdomen, the flank, and the back, on the left side. A "white spot" had appeared in the left lower abdominal area about 10 years previously and in the succeeding several months had spread rapidly to involve the

Fig. 1.—Vitiligo in (apparent) dermatomal distribution, anterior view.

area where it was observed at the time of examination. (At the time of this writing [1951] there had been no change or extension in the lesion.) The lesion caused no symptoms—there was neither history of injury to the spine nor symptoms referable to the nervous system. X-ray study of the thoracic and lumbar parts of the spine showed no abnormality. Observations on hematoxylin and eosin and pigment stains of a biopsy specimen were consistent with a diagnosis of vitiligo. Neurologic examination revealed no abnormality. Occupation did not expose the patient to chemicals known to cause pigment loss.

The lesion extended from the midline anteriorly to the midline posteriorly. The most striking feature was that the anterior border was almost a straight line and coincided roughly with the linea alba from 2 in. (5 cm.) above the umbilicus to the root of the penis. Anteriorly and laterally the lesion occupied almost the precise distribution of the ninth thoracic through the first lumbar dermatomes, whereas posteriorly the involvement was rather incomplete.[1] Small areas on the anterior and lateral aspects of the left thigh indicated minimal involvement of the second lumbar dermatome.

Fig. 2.—Vitiligo in (apparent) dermatomal distribution, posterior view.

Anteriorly there was slight extension of the lesion to the right side of the abdomen. This observation is consistent with the known fact that the sensory distribution of a dermatome extends a small distance onto the contralateral side as well as into the dermatomes immediately

1. Foerster, O.: The Dermatomes in Man, Brain **56**:1-39, 1933. Haymaker, W., and Woodhall, B.: Peripheral Nerve Injuries: Principles of Diagnosis, Philadelphia, W. B. Saunders Company, 1945.

adjacent on the same side. This case suggests that overlap is also characteristic of that function or fiber of the nervous system which influences pigment.

COMMENT

The configuration of the lesion here presented appears to be based upon either (*1*) a mechanism involving the anatomical characteristics of the central nervous system, namely, dermatomal-segmental distribution, or (*2*) pure coincidence, involving some external factor. The configuration shown does not seem explainable on a vascular basis or upon that of the diffusion of a chemical substance.

Another feature of note is that, although vitiligo is almost invariably bilateral and often symmetrical, the lesion in this case is strictly unilateral.

It is suggested, on the basis of this case, that at least some instances of vitiligo are on a neurologic basis.

SIMPLE METHOD OF MAKING X-RAY SHIELDS FOR SMALL PORTS

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AND
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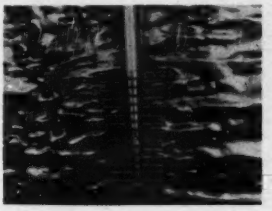
NEW YORK

A knife or scissors is generally employed to cut openings in pieces of sheet lead to make them conform to and closely shield small ports on the skin in preparation for x-ray therapy. When a circular opening is required, the use of either instrument is tedious and unsatisfactory. It is difficult to make a perfect circle with these instruments, and the cut edge is rough.



Set of graduated cork borers with plunger at top and corresponding circles made with the borers in 1 mm. lead sheet.

Recently, Wilson[1] described a means of shielding through the use of a plastic compound. We have found this method excellent in treating lesions of irregular outline. However, a small circular opening is usually adequate for a great majority of lesions measuring several centimeters or less.

The operator may be spared a great deal of time, effort, and expense if he is able to cut a hole of the proper diameter in a simple fashion. For this purpose, we have employed ordinary cork borers which may be obtained from chemical supply houses. They come in sets of various graduated sizes, and those of larger bore are available individually. A metal plunger is included with each set. The borers in the figure range in diameter from 3 mm. to 2 cm. The cylinders are open at both ends; therefore, the lesion may be seen by placement of the cylinder over the area to be treated and thus guesswork is eliminated when deciding upon the suitable size to adopt for the particular lesion. The closely graduated borers enable allowance for the exact amount of normal skin margin which it is desirable to include in the treatment. When the proper size borer has been selected, its cutting edge is placed upon the piece of lead to be employed

1. Wilson, J. W.: Shielding of Skin Against Roentgen Radiation by Plastic Compounds, Arch. Dermat. & Syph. **62**:237 (Aug.) 1950.

and with one turn of the wrist and mild pressure the opening is executed. The metal plunger, the handle of which may be seen at the top of the row of borers in the illustration, is then inserted into the cylinder to eject the cut central circle of lead from the mouth of the borer.

The size of the lead shield in which the open port is to be cut will, of course, be determined by the location of the lesion to be treated and by the diameter of the treatment cone that is employed. With the 15-cm. focal distance lead glass cones of several centimeters diameter, it is necessary for the shield to extend only beyond the perimeter of the lead-glass tube. This method is definitely useful when modern short focal distance glass cones of small diameter are employed. Often these tubes do not give sufficient selection of port size when a lesion requires very close shielding. In treatment with 30-cm.-focal-distance cones of 10- to 20-cm. diameter, the exposed skin is protected by the placement of additional pieces of lead about the port in the customary manner.

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WATER-REMOVABLE PASTE

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and
GILBERT A. BEIRNE, M.D.
SAN FRANCISCO

During the course of management of subsiding acute and subacute dermatoses and dermatitides need has been felt for a paste which could be removed with water rather than with oil. It seemed especially desirable for use between wet dressings and soaks in fairly acute eruptions, for which a lotion was considered too drying.

It is probable that such a preparation has already been described, but a review of many of the popular dermatologic texts and peridoicals has not shown this.

In this investigation a number of water-soluble vehicles were tried, but the combination which has functioned most satisfactorily as a paste and which still can be removed by warm or cool water or solution is the following:

Talc	6.5
Zinc oxide	6.5
Haldane's emulsion base	17.0

Let a mixture be made: use no oil in mixing

The proportion of emulsion base can be increased or decreased if an alteration of the consistency is desired. Haldane's emulsion base is a pleasant, creamy white water-washable base, produced by several manufacturing pharmacists. It has the following formula.[1]

Sodium lauryl sulfate	2.0
Glyceryl monostearate	9.0
Stearyl alcohol	9.0
White petrolatum	20.0
Liquid petrolatum	30.0
Butyl parahydroxybenzoate (butoben,® Merck)	0.07
Distilled water	70.0

We have used this preparation with satisfaction in treatment of the following disorders: contact dermatitis, including "hand eczemas," acutely flared cases of seborrheic dermatitis, stasis eczema, infectious eczematoid dermatitis, atopic dermatitis, indolent post-traumatic ulcerations, pustular psoriasis of palms and soles and miscellaneous conditions in which a paste was indicated.

Criterion for satisfaction was not cure of the preceding diseases. It was whether the preparation functioned as a paste and was removable in the course of soaking or other wet therapy.

From the Division of Medicine, Department of Dermatology and Syphilology, University of California, San Francisco, Dr. Frances Torrey, chairman.

1. On occasion this formula is slightly modified by various pharmacies.

When applied in thick layers, the bulk is best removed by mechanical means.

The following medications have been found to be satisfactorily incorporated in this paste in strengths in which they are popularly used: ammoniated mercury, benzoic acid, crude coal tar, coal tar solution, menthol, oil of birch tar, salicylic acid, sulfur and iodochlorhydroxyquin (vioform®).

It is suggested that others may find a paste using different water-washable bases more satisfactory than the above. In general, however, we feel that pastes incorporating such vehicles may have a place in dermatologic therapy.

424 Capistrano Avenue.

UNUSUAL SEQUELA TO CHROME ULCERATION OF THE SKIN

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WASHINGTON, D. C.

Chrome ulceration of the skin is very common among workers processing chrome ore to chromic acid, potassium and sodium chromate and bichromate and ammonium bichromate. Recently my associates and I have observed 198 persons with chrome ulceration of the skin

Button-like scar of finger, sequela of chrome ulcer.

or its distinctive scars. Of these 198 men, of whom 102 were white and 96 were Negro, in only one was there any evidence of hypertrophic scarring or keloid formation. The two main contributing factors to the production of chrome ulcerations of the skin were contact with hot liquor (sodium or potassium bichromate solutions) and contamination of a break in the skin by one of the chrome chemicals.

REPORT OF A CASE

The case presented is that of E. B. T., a 61 year old white man, who has been a production foreman in the "liquor building" of the chemical plant since 1924 except for six years when he was not employed in the factory. In 1925 he sustained a perforated nasal septum due to chrome; a chrome ulcer also occurred on the dorsal surface of the fourth finger of the left hand. The ulcer of the finger healed slowly but completely, as is usual with this type of lesion. The worker noted, however, that the scar resulting was not normal, since it tended to project above the skin and grew slowly larger within the next several months. He had noted no change in the lesion in the last 20 years.

The lesion was round, 3/8 inch (0.95 cm.) in diameter, and had an adherent finely micaceous scale on the presenting surface. The consistency of the lesion was that of hard scar tissue. It was attached to the finger by a sessile pedicle of normal but mildly erythematous skin by which

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From the Clinical Investigations Branch, Division of Industrial Hygiene, Public Health Service, Federal Security Agency.

it was freely movable over its base. There was no underlying induration. The lesion was entirely asymptomatic.

There were noted fading scars of other healed chrome ulcers on the dorsa of the fingers and hands.

Patch testing to 0.5 per cent potassium bichromate solution elicited negative reactions. The man refused removal of the lesion for microscopic examination.

HERPES ZOSTER TREATED WITH ACTH

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SAN DIEGO, CALIF.

Within the past four months I have had occasion to observe five cases of herpes zoster treated with ACTH. Three of the patients were over 50 years of age. All had relief of pain by the time they had received the third injection of ACTH. Usually 10 to 15 mg. was given at six-hour intervals. The relief had continued for two to four months, to the time of writing. One was a case of herpes zoster ophthalmicus. The course of the disease as far as the skin picture is concerned was unaltered.

Three of the cases are included in this report by permission of Dr. E. C. Leavenworth of San Diego.

Society Transactions

DETROIT DERMATOLOGICAL SOCIETY

Arthur E. Schiller, M.D., *President*
C. J. Courville, M.D., *Secretary*
Roy H. Holmes, M.D., *Recorder*

Nov. 8, 1950

Lichen Ruber Moniliformis? Presented by DR. LOREN SHAFFER and (by invitation) DR. S. H. SAUTER.

M. M., a 25-yr.-old white woman, had generalized vesicular eruption after having scarlet fever at the age of 10 yr. This cleared except for lesions on the lower legs, persistent despite varied and intensive treatment. The patient was presented before the Society on several occasions and also at the first meeting of the American Academy of Dermatology and Syphilology in Detroit, 1938 (ARCH. DERMAT. & SYPH. **38**:317 [Aug.] 1938). In 1945 (ARCH. DERMAT. & SYPH. **54**:472 [Oct.] 1946) she was presented by Dr. Hermann Pinkus, at which time Dr. Felix Pinkus called attention to the similarity of the lesions to Kaposi's case of lichen ruber moniliformis. At this time a younger brother was presented with evident epidermolysis bullosa with numerous milia. Milia were also prominent in our patient's disease at that time.

Examination shows numerous violaceous linear bands from midthigh (mainly anteriorly) to ankles bilaterally. Many of these are circinate and serpiginous, forming bizarre patterns. On the dorsum of the feet and interspersed between the bands are violaceous papules with adherent whitish scales. Pruritus is reported as moderate. No milia are apparent.

DISCUSSION

DR. JAMES R. ROGIN: I feel this is quite typical of the clinical appearance of lichen ruber moniliformis.

DR. HERMANN PINKUS, Monroe, Mich.: The pattern of the bizarre strands is narrower and flatterer than five years ago but otherwise is unchanged. I studied five biopsies while she was under my care and others were taken at Henry Ford Hospital and at the University Hospital. No definite diagnosis could be established histologically. I believe that most or all of this patient's lesions are artificial dermatitis on the soil of a latent epidermolysis bullosa with milia formation. Lichen planus or psoriasis may be present as an accessory factor and may be the stimulus for continued self-mutilation.

DR. HOWARD J. PARKHURST, Toledo, Ohio: Many of the lesions showed micaceous scales, and there were several sharply outlined patches on the scalp. I feel the possibility of psoriasis should be still considered.

DR. FRANK STILES, Lansing, Mich.: The striking arrangement of lesions, the sharply limited areas, and the resemblance to excoriations strongly suggest a factitious element which may have prolonged the disease.

Hyperpigmentation of Undetermined Origin. Presented by the staff of the service of DR. L. W. SHAFFER.

A Negro woman aged 35 yr. had hyperpigmented macules about the size of a silver dollar on each cheek for four years. These began during pregnancy, and there are no objective symptoms.

DISCUSSION

DR. E. P. CAWLEY: These patches would probably respond to treatment with paraphenylhydroquinone. It has been tried in various concentrations and is a very definite depigmenting agent when there is an excess of melanin but apparently has no effect on discoloration due to argyrosis, etc.

DR. JAMES ROGIN: I have used paraphenylhydroquinone in strengths of 5% to 15% in polyethylene glycol with good results. There is a dermatitis first, but the treatment does cause depigmentation.

Benign Cystic Epithelioma: Therapeutic Suggestions? Presented by DR. FRANK STILES, Lansing, Mich.

In this patient typical lesions about nose and eyelids appeared in increasing number for about 15 yr. Several lesions had been removed by electrodesiccation but some reoccurred and some scarring was seen. One hundred roentgen irradiation to one small area showed no change.

DISCUSSION

DR. ARTHUR SCHILLER: The use of the true desiccation current (rather than the coagulating current) will give a quicker and better result. Inserting the needle in each of the lesions and turning the current on and raising the needle until the lesion flushes is sufficient. The amount of scarring is small.

DR. CLYDE K. HASLEY: Only one or two lesions should be treated at a time by electrodesiccation, and they should be allowed to heal before others are treated.

Fixed Drug Eruption. Presented by the staff of the service of DR. L. W. SHAFFER.
Dermatitis Herpetiformis? Presented by DR. HERMANN PINKUS.
Premycotic Stage of Mycosis Fungoides? Presented by DR. EUGENE HAND.
Discoid Lupus Erythematosus. Presented by DR. A. E. SCHILLER and DR. H. H. HOLMAN.
Dermatitis Herpetiformis? Presented by DR. J. GREKIN.
Toxic Purpura. Presented by the staff of the service of DR. L. W. SHAFFER.
Mycosis Fungoides. Presented by the staff of the service of DR. L. W. SHAFFER.
Cutaneous Manifestation of Nerve Trunk? Presented by DR. EUGENE HAND.
Primary Tuberculosis? Presented by the staff of the service of DR. L. W. SHAFFER.
Lichen Sclerosus et Atrophicans in a Diabetic. Presented by DR. CLYDE HASLEY.
Lupus Miliaris Desseminatus Faciei in a Thirty-Seven-Year-Old Female for Three Years. Presented by DR. A. E. SCHILLER and DR. H. H. HOLMAN.
Porphyria of Four Years' Duration with Severe Scarring. Presented by the staff of the service of DR. LOREN W. SHAFFER.
Lymphocytoma? Elephantiasis Nostras? Presented by DR. JAMES R. ROGIN.

CLEVELAND DERMATOLOGICAL SOCIETY

Benjamin Levine, M.D., *President*
Herbert H. Johnson, M.D., *Secretary*
Harold N. Cole Jr., M.D., *Reporter*
Nov. 16, 1950

Pemphigus Vulgaris—ACTH and Cortisone Therapy in Pemphigus Vulgaris. Presented by DR. E. W. NETHERTON.

M. G., aged 39, a white man of Jewish descent, came to the Cleveland Clinic Hospital on July 21, 1950, complaining of soreness of the mucous membrane of the mouth, erosion about the umbilicus, and a few bullous lesions on the trunk. He had always enjoyed good health, and his past and family history were not significant. In October of 1949 a red, moist, well demarcated area developed about the umbilicus. In February, 1950, he experienced some pain on swallowing.

When first seen in the clinic, there was a well demarcated, bright-red moist area involving and surrounding the umbilicus. On the upper portion of the back there were two ruptured bullae. In the mouth there were numerous small vesicles and a few ruptured bullous lesions. The lesions involved the mucosa of the cheek, the soft palate, the anterior pillars of the tonsils, and the lower gum. There were a few lesions along the sides of the tongue. The inflammatory reaction about the lesions in the mouth was very slight.

A diagnosis of pemphigus vulgaris was made, and the patient was so informed. He had just recently moved to Cleveland from Chicago, and because of his apprehension regarding the diagnosis he returned to Chicago to consult his family physician. There the diagnosis of pemphigus vulgaris was made, and he was admitted to the hospital for corticotrophin therapy.

Following the administration of corticotrophin, his lesions disappeared and he was discharged to be treated as an ambulatory patient, with marked decrease in the total dosage. He had a relapse and was readmitted to the hospital and again responded favorably to corticotrophin therapy. On September 18 he returned to Cleveland to carry on corticotrophin therapy as an ambulatory patient, and he has been under observation since that time.

It has been found that as long as corticotrophin is given in the total dosage of at least 100 mg. in 24 hr., there is no recurrence. However, when the dosage is decreased below 100 mg. there is prompt recurrence of the lesions in the mouth. There has been no recurrence of the cutaneous lesions. With a recurrence, it is necessary to increase the total dosage, up to 150 mg. a day, in order to obtain satisfactory response. On two occasions there has been relapse, when the total dosage was decreased below 100 mg. The patient is now receiving 100 mg. of corticotrophin divided into four doses, every 24 hr., and in addition is taking 250 mg. of cortisone by mouth. Also, he is taking 4 gm. of potassium chloride daily, is on a very low salt diet, and is receiving 250 mg. of chloramphenicol three times a day. Shortly after his return to Cleveland, sodium arsenate, 2% aqueous solution given by hypodermic in increasing dosage, was instituted as an adjunct to the other treatment mentioned. The dose has been increased gradually up to 1.5 cc. at the present time.

There have been no constitutional symptoms. Laboratory studies have consistently shown normal findings. The hemogram has remained normal. The blood potassium and sodium estimations, which have been carried on during his treatment, as well as the eosinophil response, indicate that he is tolerating and responding to the corticotrophin and cortisone treatment in the proper manner. At the present time there are no cutaneous lesions, and the mucous membrane of the mouth is free of vesicles and bullous lesions. There has been no edema or appreciable gain in weight.

DISCUSSION

DR. BURTON PEPPERCORN: We have a patient with pemphigus who has shown marked improvement after receiving a total of 6 gm. of cortisone. At the present time he is receiving 50 mg. daily and has suffered no reactions.

DR. E. W. NETHERTON: Your patient who is receiving 50 mg. daily—how long was he treated before you could give him such a small dose?

DR. BURTON PEPPERCORN: He has been treated for two and one-half months, and for about two weeks he has been receiving 50 mg. daily.

DR. E. W. NETHERTON: A patient with rather acute pemphigus which started with oral lesions was presented at the Central States meeting. We presented him at a Cleveland Dermatological Society meeting when blisters first developed. He became much worse until most of his body was involved with erosions which cleared up after intensive corticotrophin and cortisone therapy. Then he had a relapse and died despite more therapy. The patient presented today has responded very nicely, if the dosage is kept up. I would be interested to know if the administration of corticotrophin could be stopped and he could be given cortisone alone. Corticotrophin therapy is an extremely expensive procedure and can not very well be carried on indefinitely. We are giving him arsenic therapy on the theory that it might be a valuable adjunct to the cortisone and corticotrophin therapy.

A Case for Diagnosis: Keratoderma Blennorrhagica vs. Reiter's Syndrome. Presented by DR. T. A. BALLIEN (by invitation), Crile Veterans Administration Hospital.

K. R., a white male laborer aged 33, has noted small red areas on the soles of both feet for several months. These lesions have enlarged and coalesced until the soles are now entirely covered.

One month ago his right knee became swollen and acutely painful. He had noted no swelling or pain in any other joint. Three weeks ago scaling lesions appeared on the hands and legs.

There is no history of gonorrhea.

Physical examination reveals a well developed, fairly well nourished, 33-yr.-old white man who appears acutely ill. There is a yellowish-white scaling exudate over the glans penis. Over the toes and soles and the fingers and palms there are reddish-brown papules and coalescent

areas with dense yellowish, piled-up keratotic scaling. There are similar nummular lesions on the legs and arms. There are shotty, hard lymph nodes palpable in the inguinal region. The prostate is normal in size, shape, and consistency; no fluid could be expressed.

The urogram was normal. The hemoglobin was 11.2 gm. per 100 cc. and the white blood cell count 6,400. The differential count showed the following: polymorphonuclear leukocytes 79%, lymphocytes 6%, monocytes 14%, and eosinophils 1%. The sedimentation rate was 35 mm. in one hour by the Westergren method. A smear of cutaneous lesions of the feet showed gram-positive cocci, and the culture showed hemolytic Staphylococcus aureus. Results of serologic tests of the blood were negative. The total protein content was 8.8 gm. per 100 cc., albumin 5.3 gm., and globulin 3.5 gm. The gonococcal complement-fixation test results were negative.

Roentgenograms of the knees on Nov. 9, 1950, showed a marked soft-tissue swelling involving the entire right knee joint. There was moderate osteoporosis of the knee joint.

Microscopic examination of a biopsy revealed dense keratin material. In some portions of this keratin there were markedly distorted to flattened nuclei. This keratin material extended into a small invagination within the epithelium and otherwise appeared to be firmly attached to the superficial portion of the epithelium. Within the upper corium there was an occasional focus of sparse lymphocytic perivascular infiltration.

The patient has been receiving a sulfur-resorcinol (resorcin®) lotion applied locally and salicylates for pain. There has been some improvement in the appearance of the lesions.

DISCUSSION

DR. J. E. RAUSCHKOLB: I thought this was a very interesting case. I think that from the differential standpoint we will have to consider two or three entities: an arthropathic type of psoriasis, Reiter's disease, and keratoderma blennorrhagica. Keratoderma blennorrhagica is always associated with gonorrhea and is accompanied by prostatitis, vesiculitis, or a vascular type of gonorrhea. The patient says that he had no pain on prostatic examination and that the prostatic smear was negative. He gives no history of gonorrhea and has had no urethral discharge. He is married, and his wife is perfectly well. He has a monoarticular arthritis involving the right knee. This may be a gonorrhea arthritis and is always considered so until proved otherwise. His lesions are confined pretty much to the palms and soles and have also involved the nails. There are either crusted psoriatic lesions or keratoderma. They are not hemorrhagic. There are a few lesions on his lower extremities and on his arms other than on the palms and soles. With Reiter's disease there may or may not be oral lesions, urethral discharge, and cutaneous lesions simulating keratoderma blennorrhagica. I have never seen nails such as this man has with keratoderma blennorrhagica. They are typical of the nails which I thought occurred with an acute fulminating type of psoriasis. I would like to offer the diagnosis of an acute type of psoriasis.

DR. H. J. PARKHURST: It is well known that in acute psoriasis the psoriatic eruption which is present consists of atypical lesions as a rule. These lesions would have to be accepted as atypical if taken to be psoriasis. The nails are characteristic, that is true, but the acute psoriasis that I have seen and read about has started with involvement of the joints of the fingers and toes, and in the patient presented today those joints have never been involved. That would lead me away from the diagnosis of acute psoriasis, and I would be inclined toward a diagnosis of Reiter's disease.

DR. MELVIN BRODY: There is a very marked scaling in the scalp. He also has lesions on and near his knees which have a psoriatic appearance.

DR. H. H. JOHNSON: Actually this was intended to be presented as Reiter's disease versus keratoderma blennorrhagica. His entering complaint was not his skin trouble, but was an acute monoarticular arthritis. He came in for his knee and not the skin disease primarily. The arthritis has remained monoarticular. I think, as Dr. Parkhurst says, that it would be rather unusual in psoriasis to have that severe pain in a large joint and in only one joint. I think the choice of diagnosis lies between keratoderma blennorrhagica and Reiter's disease, and we will try to find more evidence of gonorrhea.

DR. E. S. HALLINGER: I was just going to ask, and Dr. Johnson has answered my question, whether or not the arthritis preceded or followed the skin lesions. Captain Emory Ladany and

Lieutenant Colonel John D. Hughes, Medical Corps, Army of the United States (Etiologic Considerations of Keratosis Blennorrhagica—Report of a Case in which Penicillin was Used, ARCH. DERMAT. & SYPH. **54**:150-178 [Aug.] 1946) made a complete list of all the cases that had been reported. I was impressed by the fact that in psoriasis the arthritis usually follows the skin lesions. In keratoderma blennorrhagica the reverse is true. I offer that as one of the finer points in this obscure case.

DR. J. R. HASERICK: I should like to suggest taking biopsy of a lesion on the knee.

Periarteritis Nodosa. Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

D. F., a white woman aged 57, presents an eruption over the thighs and lower legs of six months' duration. Associated with this, she has noted generalized weakness and periodic malaise and fever.

On examination, the temperature is 38 C. (100.4 F.) and the blood pressure 102/60. Examination of the skin reveals numerous small petechiae scattered over the lower extremities. The petechiae are confluent, discrete, and increase in number toward the ankles. There is a background of diffuse, mottled pigmentation, which is most marked near the ankles. On the inner aspect of the left thigh are several irregular areas of ecchymosis measuring 2 to 4 cm. in diameter.

Examination of the lungs shows nothing significant. The heart size is within normal limits. There is a faint blowing systolic murmur heard over the entire precordium. The liver and spleen are enlarged, and there is edema of the lower extremities.

Urinalysis revealed numerous white blood cells and 0 to 3 red blood cells per high power field. The hemogram revealed 3,750,000 erythrocytes, with 10 gm. of hemoglobin and 4,400 leukocytes, with a differential count of polymorphonuclear leukocytes 45%, lymphocytes 50%, monocytes 2%, and eosinophils 3%. The blood Kline reaction was 2 plus, and the Wassermann reaction was negative. The lumbar puncture revealed no abnormalities. The bleeding time, clotting time, capillary fragility test, and clot retraction were within normal limits. The prothrombin time was 19 sec. The serum cholesterol was 96 mg. per 100 cc. and cholesterol esters 50 mg. No significant changes were found on examination of the contents of a sternal-bone marrow aspiration.

On histological examination of a muscle biopsy specimen skeletal muscle revealed slight chronic inflammation. The walls of the arterioles showed a diffuse fibrosis of the adventitia media and subendothelial connective tissue, with stenosis of the lumens. There was a perivascular sprinkling of lymphocytes and plasmocytes.

A course of cortisone was administered (1.5 gm. total) in August of 1950, with the disappearance of symptoms and fever. There was a recurrence of symptoms when cortisone was discontinued. Cortisone was started again on November 13.

DISCUSSION

DR. H. H. JOHNSON: I should like to mention a word of warning. This patient seemed rather excitable and a little bit incoherent. I am told that she has appeared that way before. Some of the patients who give evidence of some mental instability become much more unstable on corticotrophin or cortisone therapy, and I know of three that ended up in psychiatric wards. Two were temporarily and one not so temporarily psychotic. I think a little caution in this patient's case and observation with that in mind are indicated.

DR. G. M. STROUD: At the Mayo Clinic they have reported cerebral symptoms associated with periarteritis nodosa per se, and at autopsy changes of the brain cortex are shown. (Parker, H. L., and Kernohan, J. W.: The Central Nervous System in Periarteritis Nodosa, *Proc. Staff Meet., Mayo Clin.* **24**:43-48 [Jan. 19] 1949.)

DR. E. W. NETHERTON: In that same report in the bulletin, Dr. Lovshin reported on the peripheral neurological findings and pointed out that pain in the legs and peripheral neuritis in a patient of this type is one of the early symptoms and should arouse our suspicion that we are dealing with periarteritis nodosa. I think we ought to keep that in mind in some of these vague cases. (Lovshin, L. L., and Kernohan, J. W.: Peripheral Neuritis in Periarteritis Nodosa: Clinicopathologic Study, *Proc. Staff Meet., Mayo Clin.* **24**:48-52 [Jan. 19] 1949.)

DR. E. S. HALLINGER: Have the presenting physicians tried procaine or antihistamines?

DR. J. E. RAUSCHKOLB: I think that she received antihistamines while at the medical service, with no improvement. I believe diphenhydramine (benadryl®) was given in fairly large amounts.

DR. A. E. WALKER: Have there been any other patients with periarteritis nodosa presented before the Society treated with cortisone or corticotrophin?

DR. J. E. RAUSCHKOLB: This is the only one.

DR. E. W. NETHERTON: We had a patient whom we did not treat, but it was interesting to note, in view of the patient's pain in the legs, that he also had the symptom of an erythema-multiforme-like eruption. He had severe pain in the legs and in the muscles and went to a veterans hospital, where eventually periarteritis nodosa was confirmed. He had a very high eosinophil count. We took a muscle biopsy and were unable to find any positive evidence. They found evidence in a lymph node and also took a muscle biopsy but were not able to find vascular changes. He finally died.

Dermatitis Herpetiformis. Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

Secondary Syphilis. Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

Addison's Disease. Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

Localized Myxedema. Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

Addison's Disease. Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

Early Granuloma Inguinale. Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

Dermatitis Herpetiformis. Presented by DR. E. W. NETHERTON.

Psoriasis Guttata. Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN RAUSCHKOLB.

Epidermolysis Bullosa, Treated with ACTH. (Previously presented before the Cleveland Dermatological Society on October 27, 1949.) Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

Vitiligo with Poikilodermatous Changes. Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

A Case for Diagnosis: Erythema Induratum? Presented by DR. ALLEN E. WALKER.

A Case for Diagnosis. Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

Circinate Nodular Late Syphilid. Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

A Case for Diagnosis: Acroscleroses with Involvement of the Esophagus? Presented by DR. PAUL CHIVINGTON, DR. WILLIAM MURPHY, and DR. BURTON PEPPERCORN for DR. JOHN E. RAUSCHKOLB.

Leukemia Cutis. Presented by DR. HAROLD G. BREMERS, DR. RICHARD K. GARDNER, and DR. ULLIN W. LEAVELL for DR. H. N. COLE and DR. J. R. DRIVER.

PHILADELPHIA DERMATOLOGICAL SOCIETY

Edward F. Corson, M.D., *Chairman*

H. E. Twining, M.D., *Secretary*

Nov. 17, 1950

Xanthoma Tuberosum. Presented by DR. CARROLL S. WRIGHT and (by invitation) DR. L. JAFFE.

R. H., a white youth aged 18, well nourished and well developed, presents two soft, salmon-colored nodules, each about 1 in. in diameter, one on the extensor surface of each elbow. There is one flat, salmon-colored macule about 4 mm. in diameter on the web between the left thumb and index finger. These had their onset when the patient was 10 yr. of age. The initial lesions were the size of small peas, and were mistaken for warts. They have gradually grown to their present size. The patient was on a diet rich in dairy products and eggs, including ice cream every night and eggnog every morning, for many years. A maternal aunt has "heart trouble," the patient's twin sister, "thyroid trouble." There is no family history of cutaneous diseases.

Blood count and urinalysis results on May 4, 1950, were not remarkable. The blood cholesterol content on June 8, 1950, was 330 mg. per 100 cc.; on July 22, 284 mg.; on September 8, 314 mg., and on October 27, 190 mg.

The patient has been treated with a diet excluding eggs, dairy products, lard, pork, and animal fats. No attempt has been made to exclude traces of cholesterol or plant cholesterols. The lesions have become paler, softer, less "tight," and no longer are tender when traumatized. The blood cholesterol content has decreased from 330 to 190 mg. per 100 cc.

Xanthoma Tuberosum. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. R. EWING.

DISCUSSION

DR. IRA L. SCHAMBERG: A recent paper indicated that ACTH (pituitary adrenocorticotropic hormone) will cause hypercholesteremia.

DR. FREDERICK URBACH (by invitation): At one of the meetings of last year we discussed the matter of low-fat diet. Since then we have had occasion to study four patients, one of whom is Dr. Shaffer's patient presented tonight. This diet is practically free of fat—less than 15 gm. daily; consequently, it is also low in cholesterol. We have not had a final report on these patients, but it is our impression that if patients are given a very low-fat diet, both animal and vegetable, the serum cholesterol will fall markedly. Machella demonstrated that it is possible to lower the cholesterol content, even in normal people, about 40%. The xanthoma lesions will resolve eventually. There are reports of similar effects of other diets, particularly the Kempner rice diet, which is almost fat-free, consisting of only boiled rice and sugar. Patients on that diet will show a great fall in the blood cholesterol content.

DR. HERBERT M. LEAVITT, Easton, Pa.: Has anyone had any experience with the use of large doses of choline or inositol in patients of this type? I have seen it work dramatically in a patient with xanthoma diabeticorum.

DR. MORRIS MARKOWITZ: What would be the effect of insulin? Has anybody had any experience with it?

DR. FREDERICK URBACH (by invitation): Choline and inositol are probably very valuable adjuncts. They will sometimes lower blood cholesterol, but it is our opinion that patients receiving such treatment must be put on a low-fat diet as well.

Pemphigus Vulgaris—Cortisone Therapy. Presented by DR. M. H. SAMITZ and (by invitation) DR. R. H. WIGGALL.

S. B., a white man aged 56, presents superficial ulceration of the buccal mucosa, hard palate, and tongue. There are crusting and ulceration of the lower lip and crusted lesions on the back, chest, abdomen, and extremities. He has bullae on the dorsum of the left foot and between the toes. There is mild hyperkeratosis of the soles with fissures in each palm. There is paronychia of all the fingers. About a year and a half ago the patient noted sores in his mouth and, about six months ago, the lesions on his feet. He was admitted to the hospital in June, 1950, and received corticotrophin, 75 mg. five times a day and 50 mg. three times a day. The cutaneous lesions improved but those in the mouth only slightly. He was readmitted in August, after the reappearance of cutaneous lesions, and ACTH was again administered. Edema developed with a 10 lb. (4.5 kg.) gain in weight. The lesions again improved, but the improvement in the oral lesions was less than in the cutaneous lesions. Two weeks ago the bullae again appeared.

Seven years ago the patient suffered cerebral thrombosis with impairment of vision and deafness.

The blood pressure is 110/80. The general physical findings were not significant except for deafness.

A blood count revealed 73% hemoglobin, 3,540,000 erythrocytes, and 9,000 leukocytes. A urinalysis showed a trace of albumin. The blood urea nitrogen was 39.8. The fasting blood sugar was 115. The initial eosinophil count was 1,300 per cubic millimeter; after four hours of cortisone therapy it was 218.

The patient was treated with cortisone, 300 mg. the first day and 200 mg. the next two days, 150 mg. a day in divided doses. There was cessation of formation of bullae but only a slight change in the mouth lesions. Potassium permanganate baths and 1% iodochlorhydroxyquin (vioform®) in shake lotion were also prescribed.

DISCUSSION

DR. M. H. SAMITZ: It should be noted that this is his third admission to the hospital, and he is receiving his third course of cortisone. Corticotrophin was found to be of no help. With cortisone therapy, however, there was a remission. Previously he had had three months of treatment with potassium arsenite (Fowler's solution) and blood transfusions, but acute hepatitis and jaundice developed following a transfusion. We have given him cortisone for six months. Each course has produced a remission for about two months.

DR. DONALD M. PILLSBURY: I recently treated a patient with a severe case of pemphigus with corticotrophin. In the beginning there was decided remission of lesions, but after about a fortnight, right in the middle of treatment, she had a severe flare-up which was not affected by corticotrophin in increased doses. I therefore discontinued that treatment.

DR. M. H. SAMITZ: I might say that this man is one of five with pemphigus who are being treated with the hormone. We have a female patient who has been given cortisone continuously for five and one-half months. When we saw her first she was in the second trimester of pregnancy, and with ACTH and cortisone we were able to keep her skin fairly free of lesions so that she was delivered of a normal baby. We had expected an abnormal baby as a complication owing to the tremendous doses of corticotrophin and cortisone. She is home taking a low maintenance dose of cortisone. The other patients are in a state of remission with cortisone. Pemphigus is a capricious disease and sometimes has spontaneous remissions, but there is no question that with the hormone we have been able to help four of these five patients. In one, cortisone was of no value.

Acanthosis Nigricans. Presented by DR. CARROLL S. WRIGHT and (by invitation) DR. LOUIS JAFFE.

F. H., a Negro aged 32, presents a verrucous, soft, black patch in each axilla and in the crural and perianal regions. There is a black, velvety dermatosis on the dorsa of the hands and feet, the extensor surfaces of the forearms, and, to a lesser extent, on the rest of the forearms, legs, and thighs. The knees exhibit hard, dry skin which is not very velvety at present. There are lichenified patches on the dorsa of the feet. The patient has had the eruption as long as he can remember—at least 15 yr. It has become gradually more prominent. It started on his hands, then spread to the knees and feet. The patient did not know of its presence in his axillae. The eczematous patches on the dorsa of the feet are of four years' duration.

Examination and culture for fungi from the toes did not show significant results. The results of serologic tests for syphilis were negative. The fasting blood sugar was 138 mg. per 100 cc. and 145 mg. per 100 cc. A urinalysis on Feb. 14, 1950, showed albumin 4 plus, many hyaline and a few fine granular casts, a few leukocytes, and occasional epithelial cells. A urinalysis on July 17 revealed a faint trace of albumin and a few leukocytes and epithelial cells.

The reports on the biopsies were given. On July 25, 1949, specimen from the leg showed chronic nonspecific dermatitis. On July 17, 1950, a specimen from the right knee showed hard nevus of Unna and a specimen from the right axilla, according to Dr. Beerman, showed papilloma and no definite acanthosis nigricans although it was suggestive. Dr. Weidman reported acanthosis nigricans.

The patient has been treated with x-rays and palliative topical applications to the eczematous patches, with improvement. There has been no treatment of the other lesion.

DISCUSSION

DR. FRED D. WEIDMAN: The first case I ever saw was in a dog. At that time I was studying under Dr. Hartzell, and he received a request for consultation from the Professor of Diseases of Small Animals in the Veterinary School. The animal had the classical soft, black, velvety lesions in axillae and groins.

DR. HERMAN BEERMAN: Dr. Curth reported this condition in a dog not so long ago.

DR. FRED D. WEIDMAN: I cannot recall ever having seen a Negro with that type of skin. Also, attention is drawn to the fact that the lesions are present on the backs of the hands and that the patch on the ankle is suggestive of lichen simplex chronicus.

DR. HERMAN BEERMAN: The lesions on the backs of the hands looked like velvet. Dr. Weidman and I studied the cases illustrated in the "Corpus Iconum Morborum Cutaneorum," looking for a nevus that might agree with that type of picture, but unsuccessfully. It looks like linear nevus rather than acanthosis nigricans. The other lesion is acanthosis nigricans.

Dermatitis Herpetiformis. Presented by DR. REUBEN FRIEDMAN and (by invitation) DR. JACK WEINER and DR. JOSEPH GROPAN.

DISCUSSION

DR. MEYER L. NIEDELMAN: Dr. Weiner has presented this case for suggestions of therapy. Our experience with aureomycin in dermatitis herpetiformis has been very disappointing. Unfortunately, sulfapyridine, like the other sulfa drugs, will depress the bone marrow action and produce toxic symptoms. There are two other drugs which I may suggest. One is nicotinic acid given in high dosage, such as 100 mg. three times daily, or the sodium or potassium salt of paraaminobenzoic acid given in 10 to 15-gm. doses daily. These three drugs appear to have the same chain radical, and this probably accounts for their similar effectiveness.

DR. A. STRAUSS: I have another therapeutic suggestion. I have had experience in only one case, but it was rather dramatic. A patient with dermatitis herpetiformis had the disease for three years. She had been given all these drugs with a few remissions. I gave her vitamin B_{12}. Her lesions healed immediately, the itching stopped, and she has not had any lesions since then. The dose was 1 cc. or 30 γ.

DR. IRA L. SCHAMBERG: A patient of mine whose dermatitis has been excellently controlled for 14 mo. by sulfapyridine plus phenylazodiamino-pyridine hydrochloride (pyridium®) and nicotinic acid (niacin) had a severe exacerbation after this therapy was stopped and therapy with terfonyl® (a preparation containing equal parts of sulfadiazine, sulfamerazine, and sulfamethiazine), which was recently recommended, was started.

DR. FRED D. WEIDMAN: Is chromium sulfate by mouth, 5 grains (0.3 gm.), used any more? The last I heard, it effected two or three remissions. I have seen striking improvement from it, though the improvement lasts for only two or three trials.

DR. A. STRAUSS: One advantage of vitamin B_{12} is that it is a harmless drug, as far as I know; there are no reactions. This woman has gained in weight and looks, works, and sleeps much better.

DR. REUBEN FRIEDMAN: An interesting feature about this case is that dramatic improvement followed almost immediately upon the administration of sulfapyridine. Unfortunately, the patient began to develop signs of agranulocytosis, and we had to resort to remedies to control that. She is now being treated with sulfadiazine. I rather hesitantly gave my consent to the use of this drug, but the residents are keeping a careful watch on her progress and I think she may respond.

Ocular Pemphigus. Presented by DR. PATRICIA DRANT and (by invitation) DR. KENT FINLEY.

G. M., a white woman aged 34, presents scarring, shortening with scar-tissue formation of the upper eyelid, and symblepharon affecting the lower lid. The conjunctiva has a dried appearance. There are no symptoms of any disease of the eyeball. Retraction of the right upper eyelid was brought to the parent's attention by a photographer. Examination revealed the present condition.

DISCUSSION

DR. H. H. PERLMAN: I should very much like to know the criteria for the diagnosis of ocular pemphigus. Why cannot that be Steven-Johnson syndrome—erythema multiforme in the adult?

DR. DONALD M. PILLSBURY: Dr. Finley, an ophthalmologist, demonstrated the disease of this patient most interestingly and, to me, most convincingly. It is extraordinary that the patient had no symptoms. She is a photographer's model and became aware of the disease only because there was a retraction of the right upper lid which was revealed in a photograph.

DR. KENT FINLEY (by invitation): This case is interesting from several angles. This young woman has had no subjective symptoms. It is unusual that she had no inflammatory reaction whatever in this right eye; her photograph showed the distortion and caused her concern because of her business. She consulted an ophthalmologist who noticed the scarring of the upper cul-de-sac of the palpebral conjunctiva. When I saw her I thought of pemphigus and asked Dr. Drant to examine her, but no cutaneous lesions were found. The left eye is uninvolved. The lesions which are present in the right eye are a shortening and contraction of the palpebral conjunctiva, causing retraction of the upper lid, and in the lower lid a small symblepharon near the external canthus. In ocular pemphigus the bleb formation so common in dermatological pemphigus is not seen nearly so frequently. Apparently the reason is that the conjunctiva has less resistance than the skin and therefore bleb formation is not so apt to occur. The process then causes an inflammatory reaction with thinning, eruption, and ulceration at one point followed by scar-tissue formation with consequent contraction of that tissue and then distortion of the conjunctiva, which we have in this patient. The fundamental processes occur in the mucous membrane, that is, the tissue beneath the conjunctiva proper, and occur primarily as a formation of scar tissue. The lacrimal glands of the conjunctiva are destroyed in this formation, so that the picture resolves itself as follows: The scar continues with contraction of the conjunctiva, and the shortening causes inability of the eye to rotate properly. Since the glands are destroyed in the process, the normal secretions do not occur; the conjunctiva becomes dry and a condition is produced similar to xerosis, which we see in advanced vitamin A deficiency. Finally, ankylosis of the conjunctiva develops, in which the entire conjunctiva is dried up. The eye has no rotation, the lids are retracted, and eventually the lids cannot even close. Severe ossification of the cornea and loss of vision are late manifestations. Dr. Klauder feels that ocular pemphigus is a separate syndrome from generalized pemphigus. I do not believe that that view is held by ophthalmologists in general. Those to whom I have spoken feel that it is part of the syndrome. I have spoken to many ophthalmologists in the eastern United States concerning this particular case and have met only one who has recently seen a patient with ocular pemphigus—Dr. Allen Woods, professor at Johns Hopkins Hospital, who treated a patient with instillation of cortisone by drops. After a long period he felt that perhaps he had obtained some improvement. At the Wills Hospital (for the eye) six patients with ocular pemphigus, but all otherwise healthy people who have had the disease for a long while, are being treated. Patients have been treated with cortisone for four to six weeks, with apparently no results. I do not believe that four to six weeks is long enough, and the disease in these patients is so advanced that there would probably be no results anyway. Dr. Woods told me that Dr. Harvey has recently treated six patients with buccal pemphigus with corticotrophin. In one he thought there was some improvement. Our experience with cortisone is extremely limited. Dr. Klauder raised the question as to whether buccal pemphigus could be of virus origin and whether or not courses of aureomycin might be indicated. I have no clinical experience to go by on that, and I do not know how one would begin to treat such patients with aureomycin. My feeling would be to give this patient drops of cortisone four or five times a day and maintain therapy for perhaps a year or a year and a half; perhaps indefinitely. I do not know how else one could judge it. Cortisone could be administered systemically.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: Dr. Klauder showed a patient with ocular pemphigus with genital lesions. Have genital lesions been looked for in this patient?

DR. EDWARD F. CORSON: There are no cutaneous lesions in this patient.

DR. H. E. TWINING: I was fortunate enough to be associated with Dr. Klauder when he originally called this condition essential shrivelling of the conjunctiva. There were several patients he was following at that time, and a few eventually developed cutaneous lesions and the genital area was one of those involved. There were one or two patients in whom the ophthalmologist surgically separated the lids, which had became cicatrized and fixed with practically no mobility, but this procedure was an absolute failure. Once the wounds healed, the condition was exactly the same as before. Many here tonight have mentioned the encouraging results obtained with corticotrophin. My experience has been with only two patients, one with generalized scleroderma treated in the United States Naval Hospital. Before administration of the drug this patient was unable to smile or open his mouth very wide. During the administration of drug he improved generally and his skin became much more flexible, but the corti-

cotrophin had to be discontinued because of kidney involvement. His course was rapidly downhill and terminated in death. The other patient had disseminated lupus erythematosus, a boy of 17 with lesions on the face and body. He had leukopenia with a count of 1,300, and lupus erythematosus cells were demonstrated in the blood. The physicians decided to treat him with corticotrophin. The lupus erythematosus lesions have disappeared, but while he was taking the drug purpuric lesions developed on the lower legs, deep nodular lesions on the thighs, and eventually bullous lesions around the purpura on both legs. The nodular lesions began to fluctuate and eventually broke down. We feel in this case that the corticotrophin probably cured his lupus erythematosus but lowered his general resistance so much that he will not recover. In my opinion corticotrophin is a dangerous drug and should be used with caution.

NOTE: The patient with lupus erythematosus died. The diagnosis was pyocyaneus septicemia and acute disseminated lupus erythematosus.

DR. BENJAMIN GROSS (by invitation): At the Wills Hospital we have used aureomycin and the cutaneous lesions cleared but not the ocular lesions; they progressed. To date we have two patients with remission of the cutaneous lesions with aureomycin therapy but no changes in the ocular condition.

DR. FRED D. WEIDMAN: As we all know, pemphigus is a superficial disease, if nothing else, and I was surprised at the mention Dr. Finley made of involvement of the mucous glands in patients with ocular involvement. I should like to ask whether that involvement comes early or late. Only if it comes late can I understand it, and then as the result of fibrosing changes.

DR. KENT FINLEY (by invitation): I believe it comes late, Dr. Weidman. It is not an early symptom.

Coexisting Tinea Capitis (Audouini Type) and Alopecia Areata. Presented by DR. MEYER L. NIEDELMAN and DR. ADOLPH H. BLEIER.

Lingual Papilloma: Glossitis Rhombica Mediana? Lymphangioma? Presented by DR. MARGARET GERLACH MAHONEY and (by invitation) DR. J. F. MAHONEY.

Lupus Erythematosus Disseminatus with Parotitis and Cheilitis. Presented by DR. LEWIS M. JOHNSON, Lancaster, Pa.

News and Comment

GENERAL NEWS

Fellowship in Dermatology.—Washington University School of Medicine, accredited for three-year training by the American Board of Dermatology and Syphilology, offers a fellowship in dermatology. Training may be started at any time. Further information and application blanks may be secured from the Assistant Dean in Charge of Postgraduate Instruction, Washington University School of Medicine, 4580 Scott Ave., St. Louis 10.

Medical Motion Pictures.—A revised catalogue of motion pictures available through the Committee on Medical Motion Pictures of the American Medical Association is now ready. Copies will be sent to the secretary of each county and state medical society. This catalogue lists 62 16-mm. films, most of which are at the professional level. Fourteen of these films are suitable for showing to lay groups. Eight new films have been added. Copies are available upon request from the Committee on Medical Motion Pictures, American Medical Association, 535 No. Dearborn St., Chicago 10.

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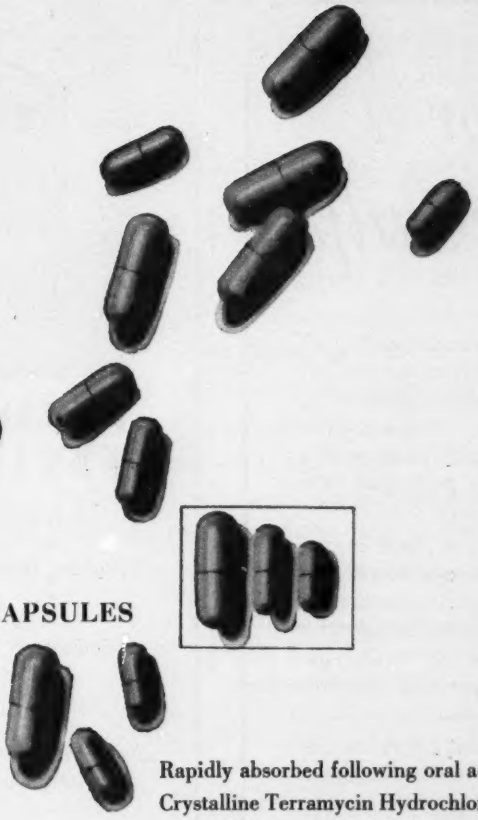

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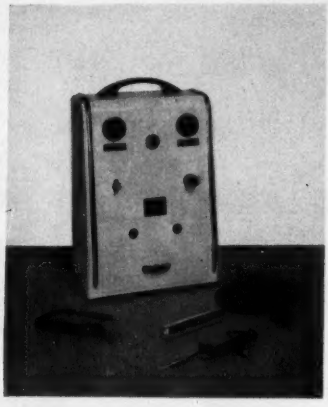

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1. Combes, F. C.: Coal Tar in Medicine. Industrial Medicine **13**:550-552 (July) 1944.
2. Combes, F. C.: Coal Tar in Dermatology. Arch. Dermat. and Syph. **56**:583-588 (Nov.) 1947.
3. Ellis, C. C.: Wooldridge, W. E., and Weiss, R. S.: J. Invest. Dermat. **10**:6 (June) 1948.

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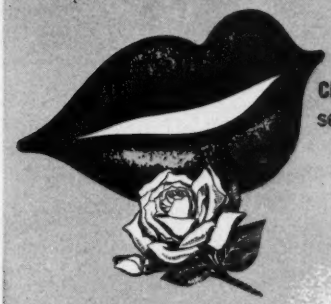

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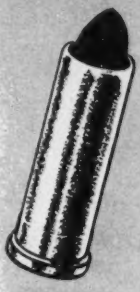

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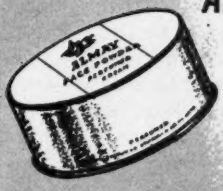

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1 Gross, Elmer R., M.D.; Wright, Carroll S., M.D.; Oral Bismuth Therapy in Syphilis and Various Dermatoses—Paper presented at the Pennsylvania Medical Society Meeting, October 8, 1946 at Philadelphia, Pennsylvania.

2 Gross, Elmer R., M.D.; Howles, James K., M.D.; Non-Specific Treatment of Dermatoses and Adjunctive Therapy of Syphilis with Oral Sodium Bismuth Triglycollamate. Read before the Section of Dermatology and Syphilology Meeting of the Centennial Meeting of the A.M.A. at Atlantic City, New Jersey, June 12, 1947.

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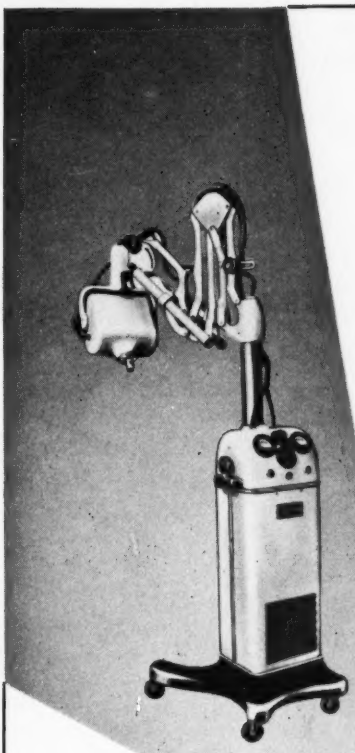

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